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PSYCHOPHARMACOLOGY ABSTRACTS

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ABSTRACTS

PRECLINICAL PSYCHOPHARMACOLOGY

02 DRUG DEVELOPMENT (PRECLINICAL SCREENING)

067120 Brink, J. J.; Cariglia, N.; Stein, D. G.; Galipeau, L. A. Department of Biology, Clark University, Worcester, Massachusetts 01610 Uptake of (14C) pentylenetetrazol by developing rat brain. ***Brain Research (Amsterdam).*** **19(3):445-450, 1970.**

It has recently been reported that various stimulant drugs, such as pentylenetetrazol (PTZ) and strychnine, can enhance learning and memory in mice and rats when given in subconvulsive doses. This has led to speculation on the brain concentrations of these drugs that may be necessary to achieve the behavioral effects and to possible correlations between these parameters. This problem has been approached on the premise that if PTZ can facilitate learning in mature rats, then it may be possible to accelerate this process by administering PTZ to rats during postnatal growth to maturity. As a first step, it seemed desirable to obtain evidence on the temporal disposition of PTZ in both the blood and brain of rats after i.p. administration and to then examine these levels after chronic pretreatment with subconvulsive doses of PTZ for different time periods during postnatal growth. The results obtained in these experiments could be useful in estimating time intervals for injections of this drug to obtain optimal behavioral effects in learning tasks or to correlate the convulsive action of the drug with cerebral levels. 14C - Labeled PTZ given i.p. to adult rats (10mg/kg) attained maximal levels in the brain within 10 minutes and was essentially all eliminated within 24 hrs. Chronic pretreatment of maturing rats with PTZ did not alter the levels found in the brain relative to untreated controls. Based on brain levels of PTZ in 5 minutes it was calculated than an effective concentration of 35 to 40 micrograms/g brain was required to initiate convulsions. The possibility that chronic treatment, developing rats with subconvulsive doses, PTZ would lead to cumulative retention and sensitization to this drug was not confirmed by our data. 12 references. (author abstract modified)

069309 Teller, David N.; Orenstein, Stuart; Horn, Babette; Denber, Michel J. A. Research Division Biochemistry Laboratory, Manhattan State Hospital, Wards Island New York, N. Y. 10035 The effects of various prior treatments upon the transport of chlorpromazine and trifluoperazine into rat brain. ***Clinical and Basic Research.*** **31(11):20-27, 1970.**

Brain and blood concentrations of chlorpormazine (CPZ) and trifluoperazine (TFPZ) are reported at various times after acute and chronic dosage into the rat brain, and the effects of various prior treatments upon the transport of CPZ and TFPZ are observed. Rats were treated with psychotropic drugs; procyclidine, mefexamide, mescaline, sodium barbital, beta-diethylaminoethyl diphenylpropylacetate hydrochloride along with CPZ and TFPZ for up to 12 days and then injected with the radioactive drug and killed. The effects of the various treatments were studied from drawn blood samples and brain examinations. 11 references.

03 MECHANISM OF ACTION - PHYSIOLOGICAL, BIOCHEMICAL AND PHARMACOLOGICAL

067243 Iwata, H.; Nishikawa, T.; Baba, A. Department of Pharmacology, Faculty of Pharmaceutical Sciences, Osaka University, Toyonaka, Osaka-fu, Japan Catecholamine accumulation in tissues of thiamine-deficient rats after inhibition of monoamine oxidase. ***European Journal of Pharmacology.*** **12(2):253-256, 1970.**

The change in catecholamine (CA) biosynthesis and the accompanying change in blood pressure, in thiamine deficient rats, were examined after intraperitoneal injection of 10mg/kg pheniprazine to inhibit monoamine oxidase (MAO) activity. Increase in the CA level (after injection of pheniprazine) was less in the cerebral cortex, brain stem, cerebellum and heart atria and ventricles in thiamine deficient rats than in control and pair fed animals. This impairedCA accumulation in the deficient rats was restored to nearly the control level by simultaneous injection of 4mg/kg of thiamine hydrochloride with pheniprazine. The lowered CA concentration in the blood and marked hypotension of thiamine deficient rats were also restored to the control level by administration of thiamine. These results indicate that the CA turnover rate has a close relationship with physical symptoms of thiamine deficiency. However, neurological symptoms, such as reduction in

spontaneous movement, tremor, turning movements and convulsions were not fully overcome by thiamine administration although they are greatly improved within 60 minutes after its injection. This is possibly due to irreversible morphological changes in the central nervous system caused by thiamine deficiency. 11 references.

067260 Bickel, M. H.; Minder, R. Medizinisch-chemisches Institut, University of Bern, Bern, Switzerland Metabolism and biliary excretion of the lipophilic drug molecules, imipramine and desmethylimipramine in the rat -- I. Experiments in vivo and with isolated perfused livers. ***Biochemical Pharmacology.*** **19(8):2425-2435, 1970.**

The biliary excretion of the lipophilic drug molecules, imipramine and desmethylimipramine, was demonstrated and the kinetics of metabolism and bilary excretion were studied. After intraperitoneal administration of imipramine (IP) to rats with bile fistula, a large part of the material was excreted with the bile. The different types, their concentrations and their distribution of the IP metabolites were measured as a function of time. Good agreement was obtained between intact, sham operated, and rats with fistulas as well as isolated perfused rat livers. Metabolic studies in the latter system were also performed with desmethylimipramine (DMI); in addition, the influence of bile salts, SKF-525-A and phenobarbital pretreatment on IP metabolism was studied. Besides large amounts of glucuronides the bile also contains unchanged IP and DMI. The bile / plasma concentration ratios of these two highly lipophilic compounds were in the order of magnitude of 50. 22 references. (author abstract modified)

067324 Reis, Donald J.; Hess, Paul; Azmitia, Efrain C., Jr. Department of Neurology, Cornell University Medical College, New York, New York 10021 Changes in enzymes subserving catecholamine metabolism in morphine tolerance and withdrawal in rat. ***Brain Research.*** **20(2):309-312, 1970.**

A study is reported which sought to demonstrate that significant changes in the activities of three enzymes involved in the synthesis of catecholamine occur during the morphine tolerance withdrawal syndrome in the rat. Changes in the activities of tyrosine hydroxylase, monoamine oxidase (MAO), and phenylethanolamine-N-methyl transferase (PNMT) were studied in female Sprague-Dawley rats given injections of morphine (doses ranging from 5mg/kg twice daily to 95mg/kg three times per day) and divided into a tolerant (killed on the 16th day 2 hours after an injection of 130mg/kg morphine) and a withdrawal (killed 48 hours after the final dose of 130 mg/kg) group. Additional animals were used as saline and naive controls. Samples of brain and adrenal gland were used for enzyme activity determinations. During tolerance there was an increase of almost 200 percent of control of tyrosine hydroxylase activity in the adrenal gland which fell back to normal 48 hours after abstinence. PNMT activity was reduced in tolerant animals when compared to naive, but not to saline injected controls, which suggested that there is an additive effect of stress of injection and morphine in reducing the activity of this enzyme. MAO activity in the adrenal gland did not change during tolerance. During abstinence, when the animals were manifesting the clinical signs of withdrawal there was a significant increase in MAO activity. 13 references.

067384 Maj, J.; Grabowska, M.; Kwiek, J. Polish Academy of Sciences, Institute of Pharmacology, Cracow, Ojcowska 52, Poland The effect of disulfiram, diethyldithiocarbamate and dimethyldithiocarbamate on serotonin and 5-hydroxyindole-3-acetic acid brain levels in rats. ***Biochemical Pharmacology.*** **19(8):2517-2519, 1970.**

Wistar rats were used in this investigation, in the whole brain and its structures, of the effect of dopamine-B-hydroxylase inhibitors on the serotonin (5-HT) level. In most cases, in whole brain, the investigated compounds (disulfiram (DS), diethyldithiocarbamate (EE), and dimethyldithiocarbamate (MM), did not significantly alter the levels of 5-HT and 5-hydroxyindole acetic acid (5-HIAA). Significant effects of DS, MM and EE on 5-HT levels in the thalamus hypothalamus, and hippocampus were noted only in a few cases. These results seem to indicate that DS, EE and MM do not affect the 5-HT level in rat brain. 17 references.

067461 Malpica, J. F.; Jurupe, H.; Campos, H. A. Laboratory of Pharmacology, University of San Marcos Medical School, P. O. Box 2694, Lima, Peru Actions of reserpine and tyramine on the acetylcholine content of brainstem, heart and blood of the rat. ***Archives internationales de Phar-***

***macodynamie et de Therapie (Gand)* 185(1):13-19, 1970.**

The actions of reserpine and tyramine on the acetylcholine content of rat brainstem, heart and blood were investigated either in the presence or absence of cholinesterase inhibition induced by physostigmine. Both reserpine (1mg/kg) and tyramine (20mg/kg) induced a significant increase in the acetylcholine content of the brainstem and the heart of the rat, which was more marked in the case of reserpine. The pattern of changes of acetylcholine content in the brainstem was similar to that found in the heart when either physostigmine, reserpine or tyramine was administered alone or combined. The combinations of reserpine and tyramine with physostigmine showed, at 60 or 120 min after the administration of the drugs, significantly greater increments in the acetylcholine content of the brainstem and heart than the ones induced by either drug alone. This effect seemed to be additive at 60 minutes for both combinations, but in the case of reserpine plus physostigmine, a potentiation was observed at 120 minutes. When physostigmine was administered alone or together with reserpine or tyramine, detectable levels of acetylcholine appeared in the circulating blood, which were much higher than the ones found with physostigmine alone when this drug was administered combined with reserpine or tyramine. No acetylcholine was detected when either reserpine or tyramine was administered alone. The fact that reserpine and tyramine are adrenergic releasers suggests the existence of a possible relationship between free catecholamines or their metabolites and increased levels to acetylcholine in tissues. 15 references.

067462 Olatunde, I. A. Department of Pharmacology, University of Ibadan, Nigeria Quantitation of the degree of antagonism of chloroquine to histamine, acetylcholine and serotonin (PA2 values). *Archives internationales de Pharmacodynamie et de Therapie (Gand).* 185(1):66-70, 1970.

The degree of antagonism of chloroquine to histamine, acetylcholine and serotonin was quantitated in isolated guinea pig ileum. Chloroquine was found to be most active against histamine and least active against serotonin. After 2 minutes of tissue antagonist contact time, the chloroquine - serotonin antagonism was calculated as 1.0, that of chloroquine - acetylcholine was 3.8and that of chloroquine - histamine, 9.1. Apparently this chloroquine antagonism as well as other chloroquine effects observed on smooth muscle contraction was probably due to its direct spasmolytic action rather than to specific antagonism of chloroquine against the spasmogenic amines. 5 references.

067598 Padjen, A.; Randic, Mirjana. Biology Division, Institute 'Rudjer Boskovic', Zagreb, Yugoslavia Some factors influencing the release of 5-hydroxyindol-3-ylacetic acid in the forebrain. *British Journal of Pharmacology (London).* 39(1):1-8, 1970.

Electrical stimulation of the midbrain raphe in adrenalectomized rats caused a significant reduction in the forebrain level of 5-hydroxytryptamine and an increase in the level of 5-hydroxyindol-3 - ylacetic acid. Electrical stimulation of peripheral sensory nerves did not influence the forebrain content of 5-hydroxyindol-3-ylacetic acid or the efflux of 5-hydroxyindol-3-ylacetic acid from the cerebral cortex, suggesting a relationship between electrical stimulation of the caudal midbrain raphe and the release of 5-hydroxytryptamine and/or 5-hydroxyindol-3-ylacetic acid in the forebrain. Rats treated with probenecid exhibited a twofold increase in forebrain 5-HIAA content while the efflux of 5-hydroxyindol-3-ylacetic acid from the cerebral cortex remained blocked. In preliminary experiments lysergic aciddiethylamide substantially reduced or completely prevented the increase in the release of 5-hydroxyindol-3-ylacetic acid in the forebrain of untreated controls with mid-brain raphe stimulation. The observed decrease in 5-hydroxytryptamine content of the forebrain of adrenalectomized rats may indicate that the biosynthesis of 5-hydroxytryptamine does not keep pace with amine release on nervous stimulation. 37 references.

067603 Mawson, C.; Whittington, H. Pharmacology Laboratory, Wellcome Research Laboratories, Beckenham, Kent, England Evaluation of the peripheral and central antagonistic activities against 5-hydroxytryptamine of some new agents. *British Journal of Pharmacology (London).* 39(1):223P, 1970.

The new antagonists for 5-hydroxytryptamine (5-HT) were compared with methysergide for peripheral and central effects. Peripheral antagonism was measured as percentage reduction of edema formation 30 minutes after intraplantar injection of 10micrograms of 5-hydroxytryptamine

following oral administration of the drugs. Central antagonism was measured by ability to reduce the number of head twitches caused by intraventricular injection of 40micrograms of 5-hydroxytryptamine in mice. The relative peripheral activities of the four compounds varied with the interval between theiradministration and the injection of 5-hydroxytryptamine. Methergoline and alpha-anilino-N-2-m-chlorphenoxypropylacetamidine hydrochloride monohydrate had much more persistent effects than methysergide and the phenylacetamidine, xylamidine. Of the three new compounds only methergoline exhibited central antagonism of 5-HT at doses close to that causing peripheral antagonism. The two acetamidine derivatives were effective only at high dosage. 5 references.

067604 McBride, A.; Turnbull, M. J. Department of Pharmacology, University of Dundee, Dundee, Scotland The brain acetylcholine system in barbitone-dependent and withdrawn rats. *British Journal of Pharmacology (London).* 39(1):210P-211P, 1970.

Female Wistar rats were made dependent on barbitone sodium (400mg/kg/day) in drinking water and withdrawn after 4 weeks by removing the barbitone sodium from the water. No change was observed in the following in either control, barbitone-dependent and 48 hour withdrawn animals: (1) acetylcholine content, cholinesterase and choline acetyltransferase activity of frozen brains; (2) ability of cerebral slices to synthesize acetylcholine; (3) the ratio of free to bound acetylcholine from freshly excised brain. The effect of physostigmine and pilocarpine on rectal temperature was studied to determine whether barbitone dependence and withdrawal affect sensitivity to acetylcholine-like drugs. The fall in body temperature produced by either drug was similar in control and withdrawn animals, but the withdrawn group exhibited a slower return to normal. A prolonged hyperthermia followed pilocarpine administration in barbitone-dependent rats while physostigmine administration was followed by a biphasic response consisting of an initial rise followed by a fall and an eventual return to normal. 4 references.

067607 Dundee, J. W.; Isaac, M. Department of Anaesthetics, The Queen's University of Belfast, Belfast, Ireland. Interaction between intravenous alcohol and some sedatives and tranquillizers. *British Journal of Pharmacology (London).* 39(1):199P-200P, 1970.

The interactions between alcohol and various soporific agents were studied in patients anesthetized with ethanol alone, without a barbiturate supplement. After chlordiazepoxide administration, more ethanol was needed to produce sleep. The increase was associated with an increase in the concentrations of ethanol in the venous blood. After pentobarbitone, less ethanol was needed to produce sleep but this difference was not significant. Blood alcohol concentration was significantly decreased. The decline of ethanol concentration in the blood following 0.8g/kg was not affected by chlordiazepoxide. Chlordiazepoxide appears to induce cerebral tolerance to alcohol while pentobarbitone has the opposite effect. 6 references.

067608 Hutchins, D. A.; Rogers, K. J. Department of Pharmacology and Therapeutics, University of Sheffield, Sheffield, England Physiological and drug-induced changes in the glycogen content of mouse brain. *British Journal of Pharmacology (London).* 39(1):9-25, 1970.

The effect of various centrally active drugs on the concentration of glycogen in mouse brain was studied. Decapitation followed by immediate freezing in liquid nitrogen yielded glycogen concentration values that were not significantly different from values obtained when mice were killed by total immersion in liquid nitrogen. A delay before freezing, caused a 46% reduction after the first minute. Hyperglycemia induced in mice by repeated administration of D-glucose solution by mouth resulted in a small but significant decrease in the concentration of brain glycogen after 120 minutes. Insulin hypoglycemia produced a small but significant decrease at 60 minutes and an equally small but significant increase at 120 minutes. Mice placed in a ventilated oven at 30 degrees to 32 degrees C or in a refrigerator at 8 degrees to 10 degrees C showed a decrease oin glycogen after 4 hours at 10 degrees C and after 8 hours at 32 degrees C. A circadian rhythm was found with respect to glycogen concentration in which the lowest value of brain glycogen corresponded with peak motor activity and body temperature. Brain glycogen was increased by all depressant drugs tested and by some drugs which had little effect on behavior (e.g. diphenhydramine, phenytoin and propranolol) or which caused excitation (e.g. caf-

feine and nialamide). Glycogen was depleted only by compounds like amphetamine or convulsions induced by bemegride. 62 references.

067613 Diaz, Pedro M. Department of Surgery, University of Puerto Rico School of Medicine, San Juan, Puerto Rico Pentylenetetrazol and ethamivan effects on brain serotonin metabolism. ***Life Sciences (Oxford).*** **9(14):831-840, 1970.**

Male Wistar rats were used to study the effect of a convulsive and a subconvulsive dose of pentylenetetrazol (PTZ) (50 and 30mg/kg, respectively) on the metabolism of brain serotonin; 25 and 15mg/kg of ethamivan (a monoamine oxidase inhibitor) were also studied. PTZ (30mg/kg i.p.)produced a moderate increase (42 percent in brain 5-hydroxytryptamine (5-HT) and a 34 percent decrease in 5-hydroxyindoleacetic acid (5-HIAA) levels. At 50mg/kg, PTZ produced a slight increase in 5-HT. The maximum increase (18 percent) was observed 45 minutes after injection. There were only slight and insignificant changes in the acid levels. Neither dosage of ethamivan produced significant changes in 5-HIAA levels. Slight changes in 5-HT levels, which were at times significant, were observed at the two dosages used. PTZ at 30mg/kg produced a marked decrease in brain serotonin turnover, but at 50mg/kg the turnover was the same as the controls. Ethamivan had no effect on brain serotonin turnover. PTZ added in vivo and in vitro in variable concentrations had no appreciable effect on rat brain monoamine oxidase activity. PTZ at 30mg/kg increased 5-HT levels in brains treated with reserpine; at 50mg/kg there was no change. These experiments confirm that PTZ alters the metabolism of brain 5-HT and that this is not a function of the seizures. 13 references.

067687 Schildkraut, Joseph J.; Winokur, Andrew; Applegate, Clarence W. Department of Psychiatry, Harvard Medical School, Boston, Massachusetts 02115 Norepinephrine turnover and metabolism in rat brain after long-term administration of imipramine. ***Science.*** **168(3933):867-869, 1970.**

The rate of disappearance of intracisternally administered tritiated norepinephrine from rat brain was decreased after a single dose of tricyclic antidepressant imipramine. During the long term administration of imipramine, the rate of disappearance of tritiated norepinephrine from brain gradually increased, and there was a concurrent decrease in the content of endogenous norepinephrine in brain. These findings may help to explain why antidepressant effects are observed clinically only after long- term treatment with imipramine. 19 references. (author abstract)

067833 Burn, J. H. Oxford, England Hypotension caused by L-dopa. ***British Medical Journal (London).*** **No. 5696:629, 1970.**

In a letter to the editor in answer to comments of D. B. Calne (21 February, 1970, P.474), J. H. Burn indicated that D. B. Calne did not sufficiently emphasize that dopamine in anesthetized cats, rabbits, and guinea pigs is a hypotensive substance. These results were confirmed by J. H. Burn and Hornykiewicz. However, if animals were given reserpine to remove noradrenaline from sympathetic terminations, then dopamine produced hypertension. Subsequent dopamine infusion restored depressor activity of dopamine. Dopamine and noradrenaline compete for receptor sites at the vessels and when dopamine occupies these sites, it results in decreased vascular tone. When patients receive large amounts of L-dopa, more dopamine seemingly is taken up into sympathetic fibers than can be converted to noradrenaline, and the nerve impulse releases a mixture of noradrenaline and dopamine. The mixture probably has less of a vasoconstrictor effect than noradrenaline alone. 2 references.

067961 Hackman, C.R.; Rosengard. S.; Vapaatalo, H. Department of Pharmacology, University of Helsinki, Helsinki, Finland Tissue distribution of chlorpromazine studied by microautoradiography. ***European Journal of Pharmacology (Amsterdam).*** **9(1):59-66, 1970.**

Labeled chlorpromazine was administered intravenously to rats. The animals were sacrificed 1, 4, 8, 12 and 24 hours later and tissue samples of lungs, trachea, bronchi, intestine, salivary glands, liver, adrenals, and sympathetic ganglia were taken. From these samples microautoradiograms were prepared by a method which did not leach out or cause a redistribution of activity. Radioactivity was found mainly in the lungs, tracheal and bronchial epithelium, intestinal epithelium, in the serous units of the salivary glands, around the central and interlobular vessels and bile ducts of the liver and in the adrenals. Activity appeared soon after drug administration in the lungs and different epithelia and somewhat later in the salivary glands, liver and adrenals. The inner layers of the lower intestine became increasingly active

and an intense activity persisted in the colon and its contents for the duration of the experiments. These findings are discussed in the light of earlier works with whole-body autoradiography on the distribution of labeled chlorpromazine. 15 references. (author abstract modified)

067962 Nair, V.; Brown, T.; Bau, D.; Siegel, S. Department of Neuropharmacology, Michael Reese Hospital, Chicago, Illinois Hypothalamic regulation of hepatic hexobarbital metabolizing enzyme system. ***European Journal of Pharmacology (Amsterdam).*** **9(1):31-40, 1970.**

Bilateral electrolytic lesions in posterior hypothalamus of male rats have been shown to suppress the activity of the liver microsomal enzyme system metabolizing hexobarbital. Lesions in the caudate nucleus, hippocampus, preoptic area or cerebral cortex did not influence the enzyme activity. The in vitro enzyme measurements in the post hypothalamic lesioned animals have been supported by in vivo measurements of hexobarbital sleep time. In the case of caudate and hippocampal lesions, barbiturate sleep time was modified without any changes in the activity of the metabolizing enzyme. It is suggested that the activity of the enzyme system is under the regulatory control of posterior hypothalamus possibly through the release of specific hypophyseal tropic hormones. This interpretation is consistent with the results from lesions, head x-radiation and hypophysectomy. 12 references. (author abstract)

067980 Vernadakis, Antonia; Clark, Carol V. H. Department of Psychiatry and Pharmacology, University of Colorado Medical Center, Veterans Administration Hospital, Denver, Colorado 80220 Department of Psychiatry and Pharmacology, University of Colorado Medical Center, Veterans Administration Hospital, Denver, Colorado 80220 Effects of prenatal administration of psychotropic drugs to rats on brain butyrylcholinesterase activity at birth. ***Brain Research (Amsterdam).*** **21(3):460-463, 1970.**

Acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) activities were determined in brain homogenates from the offspring of Sprague-Dawley rats pretreated on the 12th, 13th, 14th, and 15th days of gestation with amphetamine sulfate (1mg/kg s.c.;5 rats), chlorpromazine HC1 (3mg/kg s.c.;4 rats), or 0.9percent saline (4 rats, controls). AChE levels were found to reach adult values inthe spinal cord between 18 days of gestation and 2 days after birth, and in the cerebral cortex around 45 days after birth. There was a high DNA content found in the newborn animals as compared to lower values found at 22 and 90 days of age, which indicated the immaturity of the cerebral hemispheres at birth. Pretreatment with chlorpromazine or amphetamine affected only BuChE activity in the diencephalon midbrain and the cerebral hemispheres, the least mature of the CNS structures studied. It is suggested that these results can be interpreted to reflect either a lower number of neuroglia as compared to controls, or a lower metabolic activity in these cells. 23 references.

068163 Meldrum, B. S.; Naquet, R. Institut de Neurophysiologie et de Psychophysiologie, C.N.R.S., 31 Chemin Joseph-Aiguier, 13-Marseille, 9e, France Effects of psilocybin, dimethyltryptamine and various lysergic acid derivatives on photically-induced epilepsy in the baboon (Papio papio). ***British Journal of Pharmacology (London).*** **40(1):144P-145P, 1970.**

The effects of various hallucinogenic drugs on the motor and electroencephalographic (EEG) responses to intermittent light stimulation in conscious baboons was investigated. Psilocybin (0.5to 4.0mg/kg) and N,N-dimethyltryptamine (0.5to 4.0mg/kg) both produced marked mydriasis with an increase in spontaneous eye movements. Intermittent light stimulation at 15 or 30 minutes after psilocybin (1 to 2mg/kg) failed to provoke normal myoclonic responses or the usual cortical spikes and waves. This protective effect lasted for more than 60 minutes after 4mg/kg. Both motor and EEG paroxysmal responses to intermittent light stimulation were blocked 15 minutes after dimethyltryptamine (2 to 4mg/kg) but recovery was more rapid than after psilocybin. Methysergide bimaleate (2 to 4mg/kg) produced sedation, reduction in muscle tone and enhancement of EEG slow activities. After injection, intermittent light stimulation failed to produce myoclonus or the usual spikes and waves. The myoclonic and the paroxysmal EEG responses to intermittent light stimulation were suppressed by 2-bromolysergic acid diethylamide hydrogen tartrate (4mg/kg), while 4mg/kg methergoline reduced myoclonic responses although cortical spikes and waves persisted. 4 references.

068165 Doggett, N. S.; Spencer, P. S. J.; Turner, T. A. R. Department of Pharmacy, University of

Aston, Birmingham 4, England The pharmacological effects of ouabain administered intracerebrally to conscious mice. ***British Journal of Pharmacology (London).*** **40(1):138P-139P, 1970.**

Ouabain (0.1to 0.4micrograms in 10 microliters) was injected into the cerebral ventricles of conscious male mice. A central nervous system depression lasting 2 to 3 hours followed, and whole body hypothermia, with a maximum fall of 11 degrees Centigrade at 90 minutes, occurred. All effects were dose dependent. Higher doses of ouabain (1 to 100 micrograms) induced convulsions and death in 80% of the animals. All ouabain induced effects were completely reversed by the intraperitoneal injection of dexamphetamine (10mg/kg), or intraperitoneal desipramine (10mg/kg). Nialamide (20mg/kg intraperitoneally 2 hours beforehand) produced no reversal. Intracerebral injection of a mixture of ouabain (0.3micrograms) and dibutyryl cyclic adenosine monophosphate (25 micrograms) produced significantly less depression and hypothermia than the same dose of ouabain administered alone. The effects of intracerebral ouabain on whole brain amine levels were to increase dopamine levels by 103%, while noradrenaline and 5-hydroxytryptamine remained unchanged. Centrally administered ouabain might be an alternative tool to reserpine in the evaluation of potential antidepressant drugs. 5 references.

068166 Marley, E.; Seller, T. J. Institute of Psychiatry, De Crespigny Park, London, S.E.5, England Some effects of nicotine on the central nervous system of chickens. ***British Journal of Pharmacology (London).*** **40(1):141P-142P, 1970.**

Effects of nicotine on behavior and electrocortical activity of fowl differ from those of muscarine. Intraventricular nicotine (0.5micromoles) had biphasic effects, with no sign of muscle contracture and slow frequency (3 to 5 potentials per second) large amplitude (400 microvolt) electrocortical potentials. The effects on posture and respiration lasted 30 to 40 minutes. Respiratory effects of nicotine (0.125 micromoles) were potentiated by eserine (0.75 micromoles), and prevented by intravenous pempidine (100 micromoles/kg for 0.5micromoles nicotine). In fowls anesthetized with chloralose, intraventricular nicotine (0.5micromoles) evoked apnea for 15 to 40 seconds, and blood pressure usually rose by 25 to 70 mm mercury. Pressor effects of intraventricular nicotine lasted 1 to 2 minutes but were prolonged to 60 to 90 minutes after bilateral vagotomy and abolished by additional spinal cord division. Nicotine (0.125 micromoles) microinfused into the prosencephalon and particularly when given into the brain stem, evoked behavioral and electrocortical effects like those following intraventricular administration, but respiration and temperature were unaltered. Nicotine, like muscarine, has widespread responsive areas in the brain, although effective doses were much larger for nicotine. A short period of sleep-like behavior and electrocortical activity was induced by nicotine. 4 references.

068290 Ng, K. Y.; Chase, T. N.; Kopin, I. J. Laboratory of Clinical Science, Division of Clinical and Behavioral Research, National Institute of Mental Health, Bethesda, Md. 20014 Drug-induced release of 3H-norepinephrine and 3H-serotonin from brain slices. ***Nature (London).*** **228(5270):468-469, 1970.**

The drug induced release of 3H-norepinephrine and 3H-serotonin from brain slices has been investigated in slices of anterior corpus striatum prepared from the brains of adult rats. The brain slices were incubated with tritiated norepinephrine or serotonin. A number of psychotropic drugs were tested to assess their influence on central neurohumoral release. Several drugs were found to profoundly affect the spontaneous liberation of labelled norepinephrine and serotonin from the brain slices. Metaraminol, D-amphetamine or L-amphetamine, desipramine and reserpine produced a substantial increase in tritium efflux from the slices. In general, tritium release from sliced incubated with 3H-norepinephrine equalled or exceeded that from tissues incubated with 3H-serotonin. The effects of some other drugs are discussed. The results of the experiment support the contention that changed perisynaptic levels of specific monoamines are responsible for the psychotropic actions of compounds such as amphetamine and desipramine. 24 references.

068600 Jori, A.; Bianchetti, A.; Prestini, P. E. Istituto di Ricerche Farmacologiche 'Mario Negri', Via Eritrea, 62, 20157 Milan, Italy Relations between barbiturate brain levels and sleeping time in various experimental conditions. ***Biochemical Pharmacology.*** **19(10):2687-2694, 1970.**

A study was conducted to analyze the effect of some drugs on pentobarbital narcosis. A linear

correlation has been obtained between sleeping time and brain pentobarbital concentration 90 min after treatment of rats with 30mg/kg intraperitoneally (i.p.)of pentobarbital. Pretreatment with various drugs abolished or modified this correlation. The effect of these drugs is analysed in an attempt to identify the mechanism responsible for the modification of the pharmacological response. SKF-525A, DDT and low doses of chlorpromazine seem to act on pentobarbital sleeping time only by modifying its metabolism. Amphetamine, on the contrary, reduces the pentobarbital sleeping time by a mechanism which is not of metabolic origin. With phenobarbital pretreatment there is a modification of pentobarbital sleeping time which is the resultant of 2 different mechanisms: increased metabolism and increased sensitivity. Chlorpromazine at high doses, as well as diazepam, affect pentobarbital sleeping time without affecting pentobarbital metabolism. 25 references. (Author abstract modified)

068949 Shellenberger, M. Kent; Walaszek, Edward. Department of Pharmacology, University of Kansas Medical Center, Kansas City, Kansas Pharmacology of the central nervous system. ***In: Spiegel, E., Progress in neurology and psychiatry.*** **New York, Grune and Stratton, 1970. 495 p. (106-129).**

Much work has recently been performed on pharmacology of the central nervous system. An important topic is the role of biogenic amines including the catecholamines, 5-Hydroxtryptamine and acetylcholine relation to central nervous system function and their role in the therapeutic effects of drugs affecting the central nervous system. Psychotomimetics including THC, LSD and mescaline were studied. Central nervous system stimulants were concerned mainly with amphetamine. Research on convulsions, convulsants and anticonvulsants are reviewed. Drugs were studied that are used in mental disorders including antidepressants, and lithium. There are also reports of studies on tranquilizers, barbiturates and morphine. 214 references.

068952 Hall, James L.; Humbertson, Albert O. University of Cincinnati College of Medicine, Cincinnati, Ohio The autonomic nervous system. ***In: Spiegel, E., Progress in neurology and psychiatry.*** **New York, Grune and Stratton, 1970. 495 p. (p. 195-213).**

Topics covered in this chapter on recent studies on the autonomic nervous system are: central mechanisms, hypothalamus, ganglia, nerves, cardiovascular system including heart and muscles, histochemistry, sense organs, gastrointestinal tract, pancreas, respiratory system, urogenital system, and biochemistry and relation of drugs to these systems. Autonomic dysfunctions were found in patients with a variety of disorders. 226 references.

068978 Lal, Harbans; Shah, Hasmukh C. Dept. of Pharmacology and Toxicology, Univ. of Rhode Island, Kingston, R. I. 02881 Effect of methylchloroform inhalation on barbiturate hypnosis and hepatic drug metabolism in male mice. ***Toxicology and Applied Pharmacology.*** **17:625-633, 1970.**

The effect of methylchloroform inhalation on barbiturate hypnosisand hepatic drug metabolism was studied and it was found that a 24 hr. inhalation of methylchloroform by male mice reduced hexobarbital hypnosis but had not effect on hypnosis produced by barbital or chloral hydrate. The maximum reduction in hypnosis occurred at 24 hr after the termination of inhalation, and the hypnosis returned to the control level at 48 hr after the termination of inhalation. The effect of repeated short exposures, 4 or 8 hr/day for several days, had a cumulative effect, but a single 8 hr exposure was without effect on hexobarbital hypnosis in male mice. The supernatant fraction isolated (centrifuging homogenates at 9000 g) from livers of male mice previously exposed to methylchloroform vapor oxidized hexobarbital more efficiently, but its ability to reduce p-nitrobenzoic acid remained unaffected. The protein content of this liver supernatant fraction also was not altered after exposure to methylchloroform. 18 references. (Author abstract modified)

069052 Baumel, Irwin; DeFeo, John J.; Lal, Harbans. Section of Neurology, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06510 Alterations in brain sensitivity and barbiturate metabolism unrelated to aggression in socially deprived mice. ***Psychopharmacologia (Berlin).*** **18(3):320-324, 1970.**

A study is made to determine if the heightened neuroexcitability measured as a reduced sensitivity to barbiturates following prolonged social deprivation is related to the isolation induced ag-

gressiveness in mice. It was found that male and female mice deprived of social interactions showed increased resistance to hexobarbital narcosis. However, only the isolated males developed aggressiveness. The more rapid disappearance of hexobarbital from the whole body of isolated mice and the higher drug concentration at awakening in these animals indicate enhanced hepatic degradation with a concomitant increase in central nervous system of excitability. Development of aggressiveness in isolated male mice did not correlate temporally with the reduced response to hexobarbital. The data suggest that alterations in barbiturate sensitivity and development of aggressiveness following social deprivation have differed biological bases. 18 references. (Author abstract modified)

069062 Bliss, Eugene L.; Ailion, Janie. Department of Psychiatry, University of Utah, College of Medicine, Salt Lake City, Utah The effect of lithium upon brain neuroamines. *Brain Research (Amsterdam).* 24(2):305-310, 1970.

The effect of lithium on brain neuroamines is studied in rats in a simulation of the human situation, in which moderate amounts of lithium are given chronically for prophylactic purposes. Accordingly, rats received a diet containing lithium carbonate at 2.55g/kg of pulverized rat pellets for 14 days, and attained plasma levels of lithium of 0.5-1.0mequiv./l. Under these conditions, no laterations from controls could be demonstrated in either the absolute levels of brain norepinephrine, serotonin, and dopamine; or in the rate of metabolism of these neuromediators. This suggests that lithium may produce its therapeutic effects through means other than the general modulation of these systems in brain. 10 references. (Author abstract modified)

069344 Korty, Patricia R. School of Aerospace Medicine, Brooks AFB, Texas Some effects of D-amphetamine on carbohydrate metabolism at ground level and altitude. Springfield, Va., NTIS, AD-713726. HC:$3.00 MF:$.95.

Measurement was made of blood glucose, liver glycogen, phosphorylase, and glucose-6-phosphatase in rats treated with d-amphetamine at ground level and at a simulated altitude of 8,000 ft. An increase in blood sugar levels was obtained in drug treated animals in both environments. Altitude exposure per se also increased blood sugar levels, but the increase was not additive at altitude following drug treatment. Liver glucose-6-phosphatase activity was unaffected by drug or altitude exposure. Glycogen levels were lower in both amphetamine-treated groups, while phosphorylase activity was increased. The response of these two parameters was the same at ground level and at altitude. (Journal abstract - USGRDR)

069367 Bernardini, Albert T. School of Aerospace Medicine, Brooks AFB, Texas Interaction of chlorpromazine and tissue binding sites: preliminary studies. Springfield, Va., NTIS, AD-714851. HC:$3.00 MF:$.95.

Minced tissue from various body components of rat were subjected to equilibrium dialysis after incubation with chlorpromazine (CPZ). Radioactive CPZ (35S-labeled) was used as a tracer. Tissue binding at low concentration (0.8to 3.4micrograms/ml.)and higher concentrations (0.2to 4 mg/ml.)demonstrated binding averages. At the higher incubation concentrations, a decrease in slope estimates indicated probable secondary binding sites. (Journal abstract - USGRDR)

04 MECHANISM OF ACTION - BEHAVIORAL

067253 Hanig, Joseph P.; Aiello, Edward; Seifter, Joseph. Food and Drug Administration Bureau of Drugs DB-413, Division of Drug Biology, Washington, D. C. 20204 Permeability of the blood-brain barrier to parenteral 5-hydroxytryptamine in the neonate chick. *European Journal of Pharmacology (Amsterdam).* 12(2):180-182, 1970.

Permeability of the blood-brain barrier to parenteral 5 -hydroxytryptamine (5-HT) was investigated in neonate chicks. Animals administered 8mg/kg 5-HT entered a roosting state. They were killed in this condition 10 min after injection and the brain removed for amine analysis. Serotonin levels were significantly elevated both in whole brain and all major brain areas of the amine injected chicks. Whereas the naturally occurring concentration of 5-HT was greatest in brainstem, this area accumulated the least of the injected amine relative to endogenous concentration. Hemispheres and optic lobes of untreated chicks had about half the concentration of 5-HT present in brainstem, but injected chicks had an increase of approximately 2 and 3 times that of brainstem, respectively. This may reflect a greater ability of brainstem to convert 5-HT to 5-hydroxyindoleacetic acid. The roosting resulting from increased brain 5-HT levels seems to mimic the

depressive phase of the natural process responsible for the characteristic ongoing behavior of rapid alternation between sleep and arousal in neonate chicks. 22 references. (author abstract)

067254 Silvestrini, B.; Quadri, E. Department of Pharmacology, A.C.R. Angelini F., Viale Amelia 70, Rome, Italy Investigations on the specificity of the so-called analgesic activity of non-narcotic drugs. ***European Journal of Pharmacology (Amsterdam).*** **12(2):231-235, 1970.**

Trazodone, pentobarbital, thiopental, chlorpromazine, propionylpromazine and chlordiazepoxide were tested intravenously in mice for acute toxicity and for effects on phenylquinone writhing, motor coordination and righting reflex. Barbiturates and chlordiazepoxide suppressed the righting reflex at doses corresponding to one third of LD50, while phenothiazines and trazodone completely abolished the righting reflex only at doses close to lethal. Barbiturates did not inhibit writhing even in doses which impaired motor coordination; chlordiazepoxide inhibited writhing at doses which, though relatively high (6% of LD50), did not impair motor coordination. Phenothiazines and trazodone inhibited writhing at doses corresponding to 0.1% of LD50 and which did not, with the exception of chlorpromazine, impair motor coordination. Phenothiazines, but not trazodone, produced a condition equivalent to catatonia. 18 references. (author abstract)

067259 Svensson, T. H. Author address not given The effect of inhibition of catecholamine synthesis on dexamphetamine induced central stimulation. ***European Journal of Pharmacology (Amsterdam).*** **12(2):161-166, 1970.**

Dexamphetamine induced central stimulation in mice, measured as an increase in motility, was studied after pretreatment with inhibitors of tyrosine hydroxylase (H-44/68) and dopamine-beta-hydroxylase (FLA-63). The experiments were performed in both normal and reserpinized mice. H-44/68 almost completely inhibited the effect of dexamphetamine in both normal and reserpinized animals. It also reduced the brain levels of catecholamines. FLA-63 partly inhibited the effect of dexamphetamine in normal mice but had no effect in reserpinized animals. A small dose of DL-threo-3,4-dihydroxyphenylserine (DOPS) restored the effect of dexamphetamine in mice given FLA-63. It also raised the level of brain noradrenaline, which had been reduced by FLA-63. The results are compatible with the view, that brain dopamine is of major importance for the central stimulant action of dexamphetamine in reserpinized mice. In normal animals both noradrenaline and dopamine appear to be of importance for this effect. 25 references. (author abstract)

067299 Khruleva, L. N. Institut Vyssheu Nervnoy Deyatel'Nosti i Neyrofiziologii Akademii Nauk SSSR, U.S.S.R. /The influence of indopan on the higher nervous activity of dogs./ Vliyaniye indopana na Vysshuyu nervnuyu deyatel'nost' sobak. ***Zhurnal Nevropatologii i Psikhiatrii imeni S.S. Korsakova (Moskva).*** **70(3):389-394, 1970.**

The influence of different dosages of indopan on the higher nervous activity of dogs was studied. It showed that indopan is an active preparation and in certain doses may have a durative stimulating effect. As all the stimulators of the central nervous system, indopan possesses a 3 phasic action: in small doses (from 0.1-0.25mg/kg) it inhibits conditioned reflexes; in middle doses (0.5mg/kg and somewhat more) it acts as an expressed stimulator; in large doses (1.0-1.5mg/kg and higher) it again calls on an inhibition of reflexes. The effect of indopan depends not only upon the doses and typological features of the animal nervous system, but from the initial functional states of the higher areas of the central nervous system. 21 references. (author abstract modified)

067522 Greene, Ernest G.; Lomax, Peter. Department of Pharmacology, School of Medicine and the Brain Research Institute, University of California, Los Angeles, California 90024 Impairment of alternation learning in rats following microinjection of carbachol into the hippocampus. ***Brain Research.*** **18(2):355-359, 1970.**

Small quantities of carbachol solution or saline were injected into the dorsal hippocampus of rats. The carbachol injections resulted in a decreased ability of the animals to learn an alternation task, with carbachol treated rats making almost twice the number of errors as saline treated animals. The injections did not appear to influence choice latency. These results suggest that cholinergic neurons in the dorsal hippocampus may play a role in the learning process. 7 references. (author abstract)

067595 Nieschulz, Otto. Quellental 1, 2 Hamburg 52, Germany /Pharmacology of the active principle of betel./ Zur Pharmakologie der Wirkstoffe des Betels. *Arzneimittel-Forschung (Aulendorf).* 20(2):218-229, 1970.

Compared to arecoline, arecaidine shows only minor parasympathomimetic properties and is a well tolerated substance. Exploratory activity, motility and appetite was depressed in mice treated with arecaidine. Hexobarbital narcosis was extended. Learning an escape reaction was slightly improved in normal mice by arecaidine; in mice sedated by chlorpromazine or reactively impeded by brain lesions, the learning was considerably facilitated by arecaidine. In rats the willingness to run risks to obtain food was enhanced. Agitating properties were not observed even with larger doses. Inhibition of spontaneous activity with a concomitant increase of induced activity and the lack of agitation seems to be a characteristic effect of arecaidine. Arecaidine is formed from arecoline present in betel by chewing the nuts. Arecaidine probably is associated with the psychic changes ascribed to a betel mixture. 17 references. (author abstract modified)

067601 Miller, A. A.; Sethna, D. M.; Young, P. A. Pharmacology Laboratory, Wellcome Research Laboratories, Beckenham, Kent, England Initial suppression of the locomotor stimulant reponse todexamphetamine in rats exposed to a novel environment. *British Journal of Pharmacology (London).* 39(1):230-232, 1970.

The effect of dexamphetamine on continuous activity was studied in two groups of rats which had been used previously in activity boxes (experienced) and with naive rats (inexperienced). Whereas the locomotor stimulatory effect from the drug was evident within one hour in the experienced group, the effect was suppressed for two hours in the inexperienced group. Dexamphetamine may suppress the initial locomotor stimulant response of maximum curiosity and fear in rats placed in a novel environment which later becomes apparent. With regard to type of activity, increased rearing in inexperienced rats during the initial phase was not detected by the apparatus. 5 references.

067605 Mulas, A.; Pepeu, G. Department of Pharmacology, School of Pharmacy, Cagliari University, Italy Disappearance in rats with septal lesions of the stimulatory effect of hyoscine on exploratory behaviour. *British Journal of Pharmacology (London).* 39(1):209P-210P, 1970.

The effects of hyoscine and amphetamine on aggressiveness and hypermotility were studied in highly aggressive and hypermotile rats bearing stereotactically placed septal lesions using a symmetrical Y-shaped runway. Unoperated rats served as controls. Thirty minutes after the subcutaneous injection of hyoscine, there was an increase in the exploratory behavior in unoperated controls, while lesioned rats exhibited a decrease. Amphetamine stimulated exploratory behavior in both groups. The septum may play a role in central cholinergic pathways. 5 references.

067606 Dorr, Marian; Joyce, Daphne; Steinberg, Hannah; Summerfield, A.; Tomkiewicz, M. Departments of Pharmacology and Psychology, University and Birkbeck Colleges, University of London, London, England Persistence of dose-related behaviour in mice. *British Journal of Pharmacology (London).* 39(1):208P-209P, 1970.

Female adult mice injected with several doses of dexamphetamine -chlordiazepoxide (ratio 1:10 by weight) were tested on a horizontal wooden board with 16 evenly spaced holes and observed for the number of times they dipped their heads into the holes and the amount of walking they did across the board in 3 minutes. Both forms of activity were increased by moderate doses of the mixture, but with high doses and most doses of separate constituents, the responses were the same as in saline injected controls. One week later, the mice were tested on the same board without the drugs, and though the amounts of both kinds of activity were considerably lower, the shapes of the dose-response curves strikingly resembled those obtained with drugs on the first occasion. It appears that dose-related behavior may persist long after the original administration of drugs. 5 references.

067695 Carey, Robert J.; Salim, Anthony P. State University of New York, Upstate Medical Center, Syracuse, New York Changes in d-amphetamine reactivity resulting from septal forebrain injury. *Physiology and Behavior.* 5(2):133-136, 1970.

The effects of d-amphetamine sulfate on spontaneous activity level and food intake were studied weekly over an 8 week span in 2 groups of 6 rats each. One group was subjected to bilateral radio frequency septal lesions and the other group was composed of operated and unoperated con-

trols. The septal lesion group differed from the controls in their reactivity to the effects of amphetamine on both activity and food intake. These effects were stable over the 8 week test period and were not the result of an effect of the lesion on the behavioral baseline established with saline. 10 references. (author abstract)

067696 Green, Richard; Luttge, William G.; Whalen, Richard E. Gender Identity Research Clinic, Department of Psychiatry, University of California, Los Angeles, California Induction of receptivity in ovariectomized female rats by a single intravenous injection of estradiol-17beta. *Physiology and Behavior.* 5(2):137-141, 1970.

Sexual receptivity was induced in ovariectomized rats by a single 100microgram intravenous injection of the naturally occurring estrogen, estradiol-17beta in combination with progesterone. This dosage of estradiol required a priming injection of progesterone in order to induce maximal receptivity. Apart from this initial potentiation, within the ranges used in this study, the duration and dosage of progesterone were not found to be significant contributors to the magnitude of the observed receptivity. No receptivity was observed during the first 16 hours after the estradiol injection, but thereafter a nearly linear increase in the magnitude of receptivity was observed until an apparent maximum was reached at 24 hour after injection. The extent of testing conducted prior to a given test influenced the degree of receptivity observed during that test. 21 references. (author abstract)

067703 Falk, John L.; Burnidge, Gay K. Department of Psychology, Arizona State University, Tempe, Arizona Drug antagonism and water intake. *Physiology and Behavior.* 5(2):193-198, 1970.

Rats adapted to a 23 hour water deprivation schedule were given drugs and drug combinations to determine dose effect relations and possible antagonistic and synergistic drug actions with respect to one hour water intake. D-amphetamine and chlorpromazine produced decreases in water intake as a function of dosage. D-amphetamine with chlorpromazine combinations decreased water intake and did not yield evidence of antagonism. Phenobarbital increased water intake as a function of dosage at 20 and 40 mg/kg but decreased it back to baseline level at 80 mg/kg. D-amphetamine with phenobarbital combinations were antagonists with respect to water intake and revealed no synergism at any of the dose combinations administered. 23 references. (author abstract)

067704 Falk, John L.; Burnidge, Gay K. Department of Psychology, Arizona State University, Tempe, Arizona Fluid intake and punishment-attenuating drugs. *Physiology and Behavior.* 5(2):199-202, 1970.

Rats adapted to a 23 hour fluid deprivation schedule were injected with chlordiazepoxide either 15 minutes or 2.25 hours before a one hour drinking period. Water intake remained at baseline level. The animals were then continued on the same schedule but were adapted to 1.5% sodium chloride solution intake during the one hour drinking period in place of water. Animals were able to hydrate themselves with this solution and their one hour intake of it was equal in volume to their one hour water intake level when on the previous schedule. Chlordiazepoxide injected 15 minutes before drinking markedly increased the intake of 1.5% sodium chloride solution. Phenobarbital had a similar effect. The results are related to the punishment attenuating properties of these drugs. 21 references. (author abstract)

067713 Reinis, Stanislav. Department of Physiology, University of Ghana Medical School, Accra, Ghana Delayed learning deficit produced by hydroxylamine. *Physiology and Behavior.* 5(2):253-256, 1970.

Hydroxylamine, a substance used as mutagen in bacteria and mammalian cells, was applied to groups of mice two weeks, one week or one day before the beginning of appetitive learning, and one day after the fifteenth experimental session of the same appetitive learning. Animals injected after the fifteenth session were tested again in the same experimental situation one day, one week or two weeks after the injection. There was no change observed in the mice injected before the learning, if compared with saline injected mice. The mice injected after the completed learning showed deterioration of the performance. The longer the interval between the injection of hydroxylamine and testing, the greater the decrease of the number of conditioned responses. However, retraining was possible. 10 references. (author abstract)

067716 Fregly, M. J.; Hughes, R. E.; Cox, C. E. Department of Physiology, College of Medicine,

University of Florida, Gainesville, Florida 32601 Effect of an oral contraceptive on spontaneous running activity of female rats. *Canadian Journal of Physiology and Pharmacology.* 48(2):107-114, 1970.

Dietary administration of Enovid at 7.0mg/kg of food for 11 days to intact female rats reduced their cyclic running activity and induced changes in vaginal cytology characteristic of estrus. There was a linear relationship between the logarithm of the dose of Enovid ingested and the percent decrease in running activity from the average observed before drug administration. Dietary administration of norethynodrel, one of the two components of Enovid, at the same level for 21 days decreased the magnitude of running activity slightly but failed to affect its cyclic nature. In contrast, dietary administration of mestranol at either 0.125 or 0.54mcg/kg of food for 24 and 29 days respectively reduced running activity and increased the length of the estrus cycle. An apparent escape from the effects of chronic administration of mestranol on spontaneous running activity was observed from 20 to 30 days after beginning treatment with either dose used. The escape was characterized by a reinitiation of cyclic running activity during chronic drug administration. Elucidation of the mechanism of the escape phenomenon will require further study. 13 references. (author abstract modified)

067882 Leaton, R. N.; Utell, M. J. Department of Psychology, Dartmouth College, Hanover, New Hampshire Effects of scopolamine on spontaneous alternation following free and forced trials. *Physiology and Behavior.* 5(3):331-334, 1970.

Spontaneous alternation of rats in a T-maze was significantly reduced with doses of scopolamine of 1.2mg/kg or higher. At no dose level, was significant response perseveration found. Both controls and scopolamine injected rats alternated 100% of their free trials after either 1,3, or 5 forced trials. Scopolamine injected rats alternated significantly more when the choices were visually discriminable than when they were similar. The reduction of alternation following free trials produced by scopolamine cannot be explained solely in terms of deficits in habituation or by response perseveration tendencies. 8 references. (author abstract modified)

067884 Kasper-Pandi, Phyllis; Hansing, Ruth; Usher, David R. Rudolf Magnus Institute for Pharmacology, Vondellaan 6, Utrecht, The Netherlands The effect of dexamethasone blockade of ACTH release on avoidance learning. *Physiology and Behavior.* 5(3):361-363, 1970.

Forty eight male albino rats received 25 avoidance training trials in a shuttle box, and a second block of 25 trials after a 0 hr, 1 hr, or 4 hr interval. Half the rats were injected with 400 micrograms of dexamethasone 21-phosphate 2 hr before the first 25 trials. Animals tested after the 0 hr interval avoided most often, and tended to make more spontaneous intertrial crossings than the 1 hr group. Dexamethasone 21-phosphate blocked adrenocorticotropin release in response to the stress of training as reflected in plasma corticosterone levels, but did not affect avoidance behavior. 18 references. (author abstract)

067919 Khazan, Naim; Brown, Peter. Department of Pharmacology, Mount Sinai School of Medicine, New York, New York 10029 Differential effects of three tricyclic antidepressants on sleep and REM sleep in the rat. *Life Sciences (Oxford).* 9(5):279-284, 1970.

EEG - EMG tracings were collected from freely moving rats with chronic cortical and neck muscle electrodes for a period of five hours and after imipramine and trimipramine were given i.p. in doses of 5, 10, and 20mg/kg and desipramine was given at 2.5, 5 and 10mg/kg to investigate further the REM sleep suppressant properties of psychotropic drugs. Desipramine and imipramine treatment resulted in a significant suppression of REM sleep episodes, leaving the sleep-awake alternation intact. While desipramine decreased sleep, imipramine facilitated it. Trimipramine showed no blocking effect on REM sleep even at the highest dose. Total sleep time was significantly higher than in the control. Thus, desipramine and imipramine which have been shown to have relatively high antireserpine activity and weak antianxiety activity, suppressed REM sleep, whereas, trimipramine, which has no antireserpine activity but high antianxiety activity, did not suppress REM sleep. 11 references. (author abstract modified)

068287 Harriman, Arthur E. Department of Psychology, Oklahoma State University, Stillwater, Oklahoma 74074 Compensatory selection of magnesium sulfate by magnesium-depleted laboratory rats. *Journal of General Psychology.* 83:239-246, 1970.

The selection of magnesium sulfate solution by magnesium depleted rats has been demonstrated. The study was made to determine whether magnesium deficient rats would correct or ameliorate hypomagnesaemia by compensatory selection of a magnesium salt solution. Fluid intakes by the depleted and control laboratory rats, aged 125 days, were recorded during 30 days of Richter type tests (test fluid opposite distilled water) with .00015M and .00075M magnesium sulfate solutions. Depleted and control rats tested with the .00075M solution did not differ significantly with respect to intakes from the test solution, and neither group drank significantly more test solution than water. In contrast, depleted rats tested with the .00015M solution drank significantly more solution than did the controls. During the last 5 days of the tests, the depleted rats drank the .00015M solution at approximately twice the rate for water. Continuing signs of hypomagnesaemia in the depleted rats tested with the latter solution indicated that the preference for the solution ameliorated, but did not correct the deficiency. 15 references. (Author abstract modified)

068288 Cole, Sherwood O. Department of Psychology, Rutgers University, The State University of New Jersey, College of South Jersey, Camden, New Jersey 08102 The relationship of amphetamine-induced anorexia and freezing under a multiple CRF-EXT operant schedule. ***Journal of General Psychology.*** **83:163-168, 1970.**

The amphetamine depression of operant behavior maintained by a similar multiple continuous reinforcement (CRF) -extinction (EXT) schedule has been investigated further, and the relationship of amphetamine induced freezing to such behavior has been determined. After initial training under a CRF schedule, 3 independent groups of male albino rats were administered zero, .5, or 1.0mg/kg of amphetamine prior to 5 successive operant sessions maintained by a multiple CRF-EXT schedule. The drug significantly depressed operant performance and produced a significant amount of concomitant freezing behavior. That the results were due to the drug was demonstrated by the recovery of behavior on two subsequent distilled water injection sessions. Since the correlation between depressed operant rate and freezing was significant on 3 of the 5 drug sessions, the anorexic action of the drug may have been exaggerated by the incompatible response nature of freezing. The results, combined with those previously found in a similar task, were discussed in terms of the ordered and nonordered action of the drug. 6 references. (Author abstract modified)

068291 Molinengo, L.: Ricci-Gamalero, Silvana. Istituto di Farmacologia e Farmacognosia, Universita di Modena, Via Campi, Modena, Italy The 'staircase maze' and the 'simple staircase' in the analysis of the psychopharmacological action of CNS depressants. ***Pharmacology (Basel).*** **4(3):169-178, 1970.**

The behavior of rats in the staircase maze and in the simple staircase is used in the analysis of the psychopharmacological action of central nervous system depressants: chlorpromazine, diallylbarbituric acid, hydroxyzine, meperidine, methadone, morphine, paraldehyde, pentobarbital and reserpine. The results indicate that low doses of barbiturates or paraldehyde depress the behavior of the rat in the staircase maze without reducing the climbing speed in the simple staircase. Tranquilizers and narcotic - analgesics depress the rat behavior in the 2 tests in the same range of doses. 16 references. (Author abstract modified)

068457 Goldstein, M.; Battista, A. F.; Nakatani, S.; Anagnoste, B. Neurochemistry Laboratories, New York University Medical Center, New York, N. Y. Drug-induced relief of experimental tremor in monkeys. ***Official Journal of the American Academy of Neurology.*** **20(11):89-95, 1970.**

Drugs which affect the disposition, metabolism and biosynthesis of dopamine and serotonin were tested for their effects on the tremor intensity in monkeys with mesencephalic lesions. The tremor in the monkeys was temporarily relieved by the administration of dopa or 5-hydroxytryptophan (5-HTP). The relief of the tremor by dopa or 5-HTP was potentiated by the administration of the extracerebral decarboxylase inhibitor MK-485 or by the administration of various antiparkinsonian drugs. The inhibition of catechal methyl transferase by tropolone potentiates the dopa induced relief of the tremor and the inhibition of monamine oxidase by Catron potentiates the 5-HTP relief of the tremor. Apomorphine also causes a temporary relief of the tremor and inhibits the synthesis of striatal dopamine. The effects of various antiparkinsonian drugs were related to their anticholinergic properties and to their ability to inhibit the uptake of striatal dopamine. 15 references. (Author abstract)

068677 Reinis, Stanislav. Department of Psychology, York University, 4700 Keele Street, Downsview 463, Ontario, Canada Time-dependent learning deficit caused by hydroxylamine. ***Psychonomic Science.*** **21(3):179-180, 1970.**

A study of the time dependent learning deficit caused by hydroxylamine was conducted, in which the effect of 0.5M hydroxylamine injected intracranially on a passive -avoidance task was followed in mice. Hydroxylamine administered 24 h before the acquisition trial or earlier had no effect on performance of animals. Hydroxylamine injected 2 h before the acquisition trial impaired the performance of animals tested 24, 48, 72 h or 1 week later. Hydroxylamine injected, 1, 2, or 24 h later interfered with the performance of animals, too. The later hydroxylamine was injected, the later the impairment of performance of animals appeared. The effect of hydroxylamine is probably associated with the mutagenic action of the drug on activated DNA. 7 references. (Author abstract modified)

068765 Thor, Donald H. E. R. Johnstone Training and Research Center, Bordentown, New Jersey 08505 Chemical induction of traumatic fighting in rats. Final Report, NIMH Grant MH-17402, 1970. 11 p.

An investigation of the chemical induction of traumatic fighting in rats has been conducted, and it has been found that violent aggressive behavior (traumatic, lethal) in male hooded rats can be stimulated by the administration of commonly known drugs. The effects of morphine withdrawal and the effects of amphetamine stimulation during morphine withdrawal are summarized from 4 publications originating from research projects condcerned with the effects of these drug treatments.

069056 Butcher, R.,; Vorhees, C.; Berry, H. Children's Hospital Research Foundation and Dept. Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio 45229 A learning impairment associated with induced phenylketonuria. ***Life Sciences (Oxford).*** **9(22);1261-1268, 1970.**

The behavioral and biochemical consequences of the postnatal dietary administration of p-chlorophenylalanine (p-Ch) and phenylalanine, alone and in combination, were investigated in rats. The biochemical manifestations of phenylketonuria (PKU) have been demonstrated in the offspring when p-Ch and excess phenylalanine were fed to pregnant rats, and a learning impairment was produced in the offspring, also. Rats, weaned at 16 to 20 days of age, were assigned to diet groups by a split litter procedure. Subjects were tested in an open field 7 days after termination of the diet, and in a water maze at 70 to 80 days of age. Animals in the PKU group, (3% excess phenylalanine and 0.12% p-Ch ad lib) gained weight less rapidly than the other diet groups in experiment 1, but no significant differences in weight were evident at the time of behavioral testing. The open field performance of the animals in all groups was characterized by large within - group variability and no statistically significant differences between treatments were observed. The maze performance of the rats in the unsupplemented diet group (PFN) in experiment 1 did not appear entirely consistent with that of the other 2 control groups. Closer examination of the data prompted an experiment to confirm the differences in maze performance between the PKU and PFN groups. The rats were pair fed for 21 days on these 2 diets, and blood specimens were collected at weekly intervals during feeding. At 55 to 65 days of age, all animals were tested in the water maze. Effects on weight were nonsignficant as before, but the number of errors exhibited by the PKU group were signficantly greater than those of the PFN controls. It is concluded that biochemical and behavioral effects that closely parallel human PKU are induced in rats treated with L-phenylalanine and p-Ch. 8 references.

069063 Moltz, Howard; Lubin, Michael; Leon, Michael; Numan, Michael. Department of Psychology, University of Chicago, Chicago, Illinois 60637 Hormonal induction of maternal behavior in the ovariectomized nulliparous rat. ***Physiology and Behavior.*** **5(12):1373-1377, 1970.**

Hormonal induction of maternal behavior in the ovariectomized nulliparous rat is demonstrated. A nulliparous female rat, if kept continuously in the presence of young, will begin to behave maternally. However, she will take, on the average, some 6 or 7 days to display the behavior. In contrast, the puerperal female responds maternally as soon as the young emerge from the birth canal. This difference in latency was attributed to the characteristic action near term of a triad of hormones, consisting of estrogen, progesterone and prolactin. The attempt was made to impose this triad on ovariectomized nulliparous females. The experimental animals were administered subcutaneously estradiol benzoate, progesterone and

prolactin. The estradiol was injected from day 1 through day 11; the progesterone from day 6 through day 9; and the prolactin on the evening of day 9 and the morning of day 10. The control females, assigned respectively to 4 groups, were administered either only 2 of the 3 inductor hormones -- the vehicle in each case having been substituted for the hormone omitted -- or simply all 3 vehicles. On the afternoon of day 10, 6 normally delivered foster young, 6 to 20 hours of age, were proffered each female. Of the 10 experimental animals, each, without exception, showed full maternal behavior at between 35 and 40 hr. Not only does this represent a significant reduction in latency from the average of 6 to 7 days characteristic of untreated nulliparae, but represents as well a uniformity in time of onset closely approaching that exhibited by the puerperal female. In contrast, each of the control groups showed marked variability in onset and a significantly higher median latency. Just how estrogen, progesterone and prolactin acted to induce maternal behavior is discussed. Also discussed is the possibility of reducing even further the obtained latency of 35 to 40 hr. 28 references. (Author abstract modified)

069065 Black, William C.; Cooper, Barrett R. Section of Neurobiology, Institute for Psychiatric Research, Indiana University Medical Center, Indianapolis, Indiana 46202 Reduction of electrically-rewarded behavior by interference with monoamine synthesis. *Physiology and Behavior.* 5(12):1405-1409, 1970.

Electrically rewarded behavior in rats was found to be reduced by interference with monoamine synthesis by administration of enzyme inhibitors. In the experiments, the effects of blockade of catecholamine (CA) and serotonin (5-HT) synthesis upon electrically rewarded behavior were evaluated with 2 behavioral techniques. Comparison of free operant responding and a rate free measure suggests that interference with CA synthesis has a minimal effect on specific task performance, the effects being preponderantly exerted on an adrenergic motivational substrate. Interference with 5-HT synthesis produced no effect on performance or motivation in this study. 20 references. (Author abstract modified)

069066 McGaugh, James L.; Krivanek, Jara A. Department of Psychobiology, School of Biological Sciences, University of California, Irvine, California 92664 Strychnine effects on discrimination learning in mice: effects of dose and time of administration. *Physiology and Behavior.* 5(12):1437-1442, 1970.

The effects of dose and time of administration of strychnine on discrimination learning in mice were studied. Results indicated that the drug facilitates learning at some dose levels. The first experiment examined the dose response effects of posttrial injections of strychnine sulphate (0.012-1.25mg/kg) on learning in mice. Injections were given each day immediately after 3 massed training trials on a food reward visual discrimination task. Facilitation was found with low (0.25,0.05,0.10mg/kg) and high (1.0and 1.25mg/kg) doses, but not with intermediate doses (0.20,0.40,0.80mg/kg). Experiment 2 examined the effects of time of pre- or posttrial drug injection intervals of 2 hour or less. With 1.0mg/kg facilitation was obtained with all pretrial injection times examined (longest interval was one hr). With 0.10mg;kg significant facilitation was obtained with injections given 30 min but not 60 min pretrial. These findings are interpreted as providing further evidence that strychnine facilitates learning by affecting posttrial neurobiological processes underlying memory storage. 32 references. (Author abstract modified)

069067 Schmidt, Hans, Jr.; Summe, James P.; Coby, William F. Xavier University, Cincinnati, Ohio Phenobarbital withdrawal and behavioral disruption in the rat. *Physiology and Behavior.* 5(12):1473-1479, 1970.

Rats given 70mg/kg phenobarbital for 15 days after learning a locomotor response show only gradual improvement in responding when the phenobarbital is withdrawn. A 5 day delay without practice resulted in very similar improvement as is gained by practice. This indicates a spontaneous diminution of a withdrawal effect which retards behavior. Comparable findings were obtained during the treatment period itself indicating an evoluation of the response contingent upon the response to the drug. Other reported experiments employed training under the influence of phenobarbital. One experiment found insignificant improvement in responding after a 7 day delay as compared with no delay. The final experiment found marked improvement in responding after 7 and 30 day delays as compared with no delay. This latter result suggests that there is a time dependent factor which directly interferes with

responding during barbiturate withdrawal. While the data do not totally negate state dependent learning, some methodological issues about it are raised. 13 references. (Author abstract)

069069 Masur, Jandira; Khazan, Naim. Faculdade de Ciencias Medicas da Santa Casa, Departmento de Ciencias Fisiologicas, R. Cesario Mota 112, Sao Paulo, Brazil Induction by Cannabis sativa (marihuana) of rhythmic spike discharges overriding REM sleep electrocorticogram in the rat. *Life Sciences (Oxford).* 9(22):1275-1280, 1970.

Changes in the electrocorticogram induced by Cannabis sativa (marihuana) during longitudinal study of the sleep -awake cycle in the rat are studied. Acute and chronic changes were detected. Adult female rats were chronically implanted with cortical and muscle electrodes for recording of the electroencephalogram (EEG) and electromyogram (EMG). The light cycle in the experimental environment consisted of 16 hours of light and 8 hours of dark. After a correlation was established between the behavioral states of sleep, rapid eye movement (REM) sleep and wakefulness and the recordings of EEG and EMG activity, tracings were collected for 12 days from 9:00 AM to 5:00 PM daily. On the fourth through the twelfth days the rats received 10mg/kg Cannabis extract by intraperitoneal injection. The extract, by test, was 1/3 as potent as delta 9-tetrahydrocannabinol (delta 9-THC). It was found that Cannabis extract induced bursts of polyspikes in the electrocorticograph of all 5 rats. These abnormal rhythmic discharges of the EEG override REM sleep episodes and occur in the rate treated both acutely and chronically with a marihuana extract and delta 8-THC. 24 references.

069074 Fekete, Marton; Kurti, Marianne. Research Institute for Pharmaceutical Chemistry, Budapest 4/1. Hungary Psychopharmacologic effects of some cholinesterase inhibitors in comparison with imipramine. *Psychopharmacologia (Berlin).* 18(3):238-248, 1970.

Results from a study conducted to determine whether some cholinesterase inhibitors exhibit psychopharmacological effects similar to those of imipramine, it was shown that imipramine, physostigmine, neostigmine and dyflos inhibited the catalepsy elicited by tetrabenazine, chlorpromazine and bulbocapnine respectively. This inhibition was demonstrable only at a given dose interval in certain cases. Both imipramine and cholinesterase inhibitors tested enhanced the hypermotility caused by amphetamine in mice, but not in conditioned rats. The effect exerted by chlorpromazine on conditioned reflex activity was inhibited by neostigmine and physostigmine. The results were discussed in relation to the effect produced by cholinesterase inhibitors on the permeability of the blood - brain barrier, and in relation to the possible significance of the cholinergic affinity of imipramine on its pharmacological effects. 40 references. (Author abstract modified)

069075 Rosen, A. J. University of Illinois at Chicago Circle, Chicago, Illinois Effects of amobarbital sodium on the acquisition and extinction of a lever-press spatial discrimination in the rat. *Archives Internationales de Pharmacodynamie et de Therapie (Gand).* 188(1):112-118, 1970.

The effects of amobarbital sodium in the acquisition and extinction of a lever press spatial discrimination were investigated in a study in which 2 groups of rats (n = 7) were the subjects. Sixty acquisition trials (6/day) 30 to positive stimulus, (S+) and 30 to negative stimulus (S-), followed by 24 extinction trials, 12 to S+ and 12 to S-, in a lever press spatial discrimination paradigm in a Skinner box. One group was treated withamobarbital sodium 10 min prior to the beginning of each daily test session, and the other group received equivalent volume injections of isotonic saline. The drug improved discrimination performance, but it did not effect rate of acquisition. Superior performance by drugges Ss resulted primarily from increased response rates to S+. An enhancement of responding to S- early in acquisition was also noted. Differences in extinction were minimal when terminal acquisition differences were eliminated. Results are discussed in terms of intervening variable as opposed to pure S - response interpretations. 8 references. (Author abstract modified)

069076 Niemegeers, C. J. E.; Verbruggen, F. J.; Janssen, P. A. J. Janssen Pharmaceutica, B-2340 Beerse, Belgium The influence of various neuroleptic drugs on noise escape response in rats. *Psychopharmacologia (Berlin).* 18(3):249-259, 1970.

The effects of 20 neuroleptic drugs on noise escape behavior were studied in rats trained to interrupt an aversive noise (95 decibels recycling every 20 sec) by jumping, in a shuttle box, from one compartment into the other. All 20 drugs pro-

longed the latency (T) and reduced the frequency (F) of the noise escape response rate. Under the described experimental conditions, the decreasing or equivalent order of potency of the 20 neuroleptics studied was: spiroperidol, spirilene, trifluperidol, benperidol, droperidol, spiramide, clofluperol, moperone, perphenazine, haloperidol, fluphenazine, amiperone, trifluperazine, pimozide, thioperazine, triflupromazine, fluanisone, chlorpromazine, pipamperone, and thioridazine. For all compounds tested, T was more sensitive to drug effect than F. Using the F 45/T 900 ratio, the order of specificity of the compounds studied was determined and is reported. As far as potency was concerned, there was a good correlation (r = 0.974) between the F 900 values of the noise escape test and the values for effective dose for 50% of the animals in the nondiscriminated Sidman avoidances test in rats and, as far as sedative properties were concerned, between the F45/T900 ratio and the palpebral ptosis/catalepsy ratio (r = -0.960) of the observation test in rats. Noise escape behavior in a shuttle box is relatively easy to obtain and stabilize in rats. Standardized, it offers a convenient method of the routine evaluation of the potency and specificity of neuroleptic drugs. 21 references. (Author abstract modified)

069077 Jones, B. J.; Tolman, B. D.; Roberts, D. J. Department of Pharmacology, School of Pharmacy, Park Road, Portsmouth, Hampshire, England Studies on interactions involving antidepressive and other drugs with tetrabenazine and noradnamine on locomotor activity in mice, including details of the experimental design and statistical analysis. *Psychopharmacologia (Berlin).* 18(3):288-299, 1970.

Studies are made on interactions involving antidepressive and other drugs with tetrabenazine and noradnamine on locomotor activity in mice. Details of the experimental design and statistical analysis are presented, and the method for measurement of the drug interactions is described. The experiments were designed on a factorial basis and the data obtained were subjected to variance analysis. Using the principles described, the effects of various drugs on the hypoactivity induced by noradnamine or tetrabenazine were studied. Twenty potential drug interactions were examined, but only 7 of these exhibited statistically significant interaction. Tetrabenazine hypoactivity was antagonized by nortriptyline, amitriptyline, nialamide and noradnamine. The latter also potentiated the effect of a low dose of tetrabenazine. Hypoactivity induced by noradnamine was antagonized by amitriptyline and nortriptyline, potentiated by atropine but unaffected by nialamide. The significance of these findings is discussed. 22 references. (Author abstract modified)

069078 Battig, K. Institut fur Hygiene und Arbetsiphysiologie, Eidgenossische Technische Hochschule, Clausiusstrasse 25, CH-8006 Zurich, Switzerland Differential effects of nicotine and tobacco smoke alkaloids on swimming endurance in the rat. *Psychopharmacologia (Berlin).* 18(3):300-340, 1970.

Differential effects of nicotine and tobacco smoke alkaloids were demonstrated in swimming endurance tests with rats. The swimming endurance of rats in a water tub was measured until the animals submerged for 2 seconds under the water surface. The total alkaloid fraction extracted from cigarette smoke produced deterioration of performance in doses of 0.05 to 0.2mg/kg.,whereas pure nicotine (0.1and 0.2mg/kg), as well as nicotine pretreated analogously to the extraction process of the total alkaloids produced performance improvements. 7 references. (Author abstract modified)

069079 Driscoll, P.; Battig, K. Institut fur Hygiene und Arbeitsphysiologie, Eidgenossische Technische Hochschule, Clausiusstrasse 25, CH-8006 Zurich, Switzerland The effect of nicotine and total alkaloids extracted from cigarette smoke in avoidance behavior in rats under extinction procedure. *Psychopharmacologia (Berlin).* 18(3):305-313, 1970.

The effect of nicotine and total alkaloids extracted from smoke on the avoidance behavior of rats under extinction procedure has been measured in an experiment extended over a period of 3 months. There was no significant difference between the 2 substances, with both inhibiting the extinction of avoidance response to approximately the same degree. Significance against the control was achieved with all treatments, the effect being significantly greater with the dose of 0.2mg/kg than with the 2 doses of 0.1or 0.05mg/kg. 14 references. (Author abstract)

069080 Bainbridge, J. G. Imperial Chemical Industries Ltd., Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire, England The inhibi-

tory effect of amphetamine on exploration in mice. ***Psychopharmacologia (Berlin).*** **18(3):314-319, 1970.**

Amphetamine has been shown to decrease exploratory activity in mice at moderate doses. The conditions under which it causes increased motility are defined as follows: dose levels abot 10mg/kg in combination with either 1) an explored environment, or 2) the grouping of several animals in one cage. The measurable sedative effect of amphetamine, demonstrated in mice, is probably very important from the point of view of extrapolating laboratory results to man. 13 references. (Author abstract modified)

069311 Wise, C. David; Berger, Barry D.; Stein, Larry. Wyeth Laboratories, Box 8299, Philadelphia, Pa. Serotonin: a possible mediator of behavioral suppression induced by anxiety. ***Clinical and Basic Research.*** **31(11):34-37, 1970.**

To test the hypothesis that drugs which increase central serotonergic activity should increase conditioned suppression of behavior, while drugs that decrease serotonergic activity should decrease conditioned suppression, rats were used in an experiment which suppressed a simple approach response by the use of a mildly painful electric shock and then an attempt was made to modify the intensity of the suppression with serotonergic drugs. The results were consistent with the hypothesis that serotonin increases behavior suppression. Depletion of central stores of serotonin by p-chlorophenylalanine or blockade of serotonergic receptors by LSD-25 greatly reduced conditioned suppression. However elevation of the level of serotonin in the brain by the combination of pargyline and 5-hydroxytryptophan significantly increased conditioned suppression. 27 references.

069333 Jeter, Ronald D; Hurst, Charles M. Texas University, Arlington, Texas Effects of staphylococcal enterotoxin B on complex operant behavior in monkeys. Springfield, Va., NTIS, AD-712396, 1970. HC:$3.00 MF:$.95.

Four female rhesus macaques (Macaca mulatta), weighing 4.31 to 5.45 kg.,demonstrated significant performance decrements following gastric infusion of 20 micrograms per kilogram of staphylococcal enterotoxin B on shock avoidance schedules (CA and DA) judged high activity, high concentration, and on positive reinforcement schedule (VISAC) and (DRL) judged medium activity, high concentration, and low activity, medium concentration, respectively. Results, obtained under a controlled atmosphere of 10,000 feet simulated altitude and 100 percent oxygen, indicated individual toxicological effects on behavior with avoidance schedules showing a stress level difference. (Journal abstract - USGRDR)

05 TOXICOLOGY AND SIDE EFFECTS

068167 Pickett, R. D. Department of Pharmacology, Welsh National School of Medicine, Cardiff, Wales Acute toxicity of heroin, alone and in combination with cocaine or quinine. ***British Journal of Pharmacology (London).*** **40(1):145P-146P, 1970.**

The acute toxicity of heroin, alone and in combination with cocaine or quinine, was determined for male white mice by injection into the tail vein until fatal collapse occurred. Control mice were injected with an equal volume of saline and killed by neck dislocation. The lungs were removed from all animals and weighed. The acute toxic dose of heroin hydrochloride was 56.7mg/kg; the lung weight of 5.59 g/kg did not differ from that of controls. The mean lethal dose for cocaine hydrochloride was 30.7mg/kg and for quinine hydrochloride, 137.8mg/kg. The toxicity of mixtures of solutions containing cocaine and heroin in fixed percentages of their respective lethal doses was determined. Low proportions of cocaine were found to antagonize the lethality of high proportions of heroin, while high proportions of cocaine potentiated the lethality of low proportions of heroin. A mixture of equal parts by weight, generally used by addicts, potentiated the lethality of heroin. The lethality of combinations of heroin with quinine was chiefly additive. Quinine alone caused an increase in lung weight over controls; this was sometimes enhanced when it was given with heroin. 4 references.

069312 Roizin, L.; Akai, K.; Lawler, H. C.; Liu, J. New York State Psychiatric Institute, Bronx, N. Y. Lithium neurotoxicologic effects: 1. acute phase (preliminary observations). ***Clinical and Basic Research.*** **31(11):38-44, 1970.**

Preliminary studies on the acute phase following intravenous infusion of high doses of lithium chloride in rats are reported. The neurotoxicological effects of lithium salts were examined. It was found that: a) the membrane unit systems compartmentalize the structural organization of the organelles; b) they maintain an orderly arrange-

ment of some of the enzyme assemblies; c) they channel the intermediary metabolites or histometabolic process and d) they regulate the ionic flux. Further elucidation of these phenomena are under investigation. 38 references.

06 METHODS DEVELOPMENT

067199 Kang, Sungzong; Green, Jack Peter. Department of Pharmacology, Mount Sinai School of Medicine, New York, New York 10029 Correlation between activity and electronic state of hallucinogenic amphetamines. ***Nature (London).*** **226(5246):645, 1970.**

The total valence electron charge density, frontier electron density, dipole moment, total energy and all energy levels of 13 hallucinogenic amphetamines were calculated using the INDO (intermediate neglect of differential overlap) method. All results were subjected to sequential multiple regression analysis. Tables illustrate the high degree of correlation between hallucinogenic activities in man and the energy of the highest occupied molecular orbital; however, 2, 3, 6 - trimethoxy, and 2, 4, 6-trimethoxy, and 4-methoxy derivatives are notable exceptions. 9 references.

067212 Bowen, D. A. L.; Gurr, D. M.; Oppenheim, G. B. Charing Cross Hospital Medical School, London, W. C. 2, England Thin layer chromatographic laboratory analysis in cases from a drug addiction center. ***Clinical Toxicology.*** **3(1):89-95, 1970.**

Laboratory analyses of urine specimens from mature, working adult drug addicts and from patients on a withdrawal program were performed. Urine must be adjusted to a pH at which the drugs are least soluble and the sample is extracted with organic solvent. Silica gel thin layer chromatography is done on the final residue after which it is air dried and sprayed for amphetamines with ninhydrin and iodoplatinate reagent for morphine and methadone. Cocaine, codeine and diphenhydramine among other addicting drugs can also be identified. The potential misinterpretations and hazards of laboratory analysis and thin layer chromatography are reviewed. Results should best be seen when a series is done over several months on an individual patient. 7 references.

067599 Dorr, Marian; Joyce, Daphne; Katz, D. M.; Marshall, I.; Steinberg,Hannah; Stolerman, I. P. Department of Pharmacology, University College, Gower Street, London, W. C. 1, England Laboratory experiments suitable for practical classes in psychopharmacology. ***British Journal of Pharmacology (London).*** **39(1):246P-247, 1970.**

Practical classes in psychopharmacology have been designed to acquaint students with a number of simple, flexible techniques which can be used for a wide range of purposes, and ultimately to illustrate principles of general significance in psychopharmacology and to stimulate the students' interest. Apparatus for testing the effectsof drugs and of other factors on different aspects of unlearned behavior such as Y-mazes, hole boards, open fields, cages for observing aggressive behavior, and apparatus for measuring ataxia were used for analysing responses to novelty, emotionality, fear, aggression, memory, learning and habituation. The effects of drugs on learned 'operant' responses and concurrent electrophysiological changes were demonstrated, as well as withdrawal from morphine.

067600 Gartside, I. B.; Harrison-Read, P. E. Departments of Physiology and Pharmacology, University College, Gower Street, London, W. C. 1, England Recording evoked potentials in the conscious rat: the maintenance of a constant behavioural baseline. ***British Journal of Pharmacology (London).*** **39(1):247-248P, 1970.**

In an attempt to stabilize the factors which cause variation in mass potentials, recordings were made from animals engaged in a task which induced constant movement and orientation towards a source of sensory stimulation. Hungry rats trained on a ratio schedule of reinforcement were trained to press a translucent panel with their snouts in order to obtain food. Variable ratio schedule typically produced very high baseline rates of response. Since the food pellet was delivered into a tray below the panel, the rats kept their heads and eyes but not necessarily their attention towards the panel. Therefore, photic stimuli for evoking visual responses were produced by a flash unit delivered to the rat through the translucent panel. Ratio schedules were relatively insensitive to treatments which did not produce motor impairment once established. This control distinguished drug effects from naturally occurring behavior. 5 references.

067892 Balagura, Saul; Devenport, Lynn. Department of Psychology, University of Chicago,

Chicago, Illinois Taste preferences: an apparatus for random and simultaneous presentation of several solids and solutions. *Physiology and Behavior*. 5(3):375-376, 1970.

A description of a preference testing experimental chamber thatpermits random and simultaneous presentation of several solid and liquid samples is presented. Some results obtained using this device are given. 5 references. (author abstract modified)

CLINICAL PSYCHOPHARMACOLOGY

07 EARLY CLINICAL DRUG TRIALS

067375 Puyelo, R.; Moreau, S.; Miedzyrzecki, J. Groupement d'Etudes de Psychiatrie Infantile de la Region de Toulouse, Toulouse, France /Testing of sulpiride in child psychiatry./ Experimentation du sulpiride en pedo-psychiatrie. *Semaine des Hopitaux de Paris (Paris).* 46(29B):93-96, 1970.

Sulpiride, which as both thymoleptic and neuroleptic properties, was tested in 2 groups of pediatric patients. The first group, 25 preadolescent and adolescent children (11 to 17 years) with conditions of intellectual, psychomotor or affective inhibition, were observed for 60 to 80 days on an outpatient basis. These were further divided into 3 groups according to dosages of drug, 100, 150 and 450mg orally per day. Placebo controls were included. The second group was comprised of 11 children (7 to 12 years) with prepsychotic and infantile psychotic conditions, treated on an ambulatory and hospitalized basis and observed for 60 to 80 days. Drug dosage was 200 to 450mg sulpiride orally per day. Drug associations were made in 4 cases with diazepam, propericiazine, haloperidol, pipamperone. In the first group the anxiolytic, disinhibitory and antidepressive properties of the drug were confirmed. In the second group, diazepam, propericiazine and haloperidol, were associated in 4 out of the 11 cases. The families, educators and medical staff noted improvement of expression, better adaptation to reality, reduction of anxiety, a stimulant effect on mood, and improvement in common movements. The whole context permitted a better educational and psychotherapeutic approach. (author abstract modified)

067666 McDowell, Fletcher; Lee, John E.; Swift, Thomas; Sweet, Richard D.; Ogsbury, James S.; Kessler, Jeffrey T. 1300 York Avenue, New York, New York 10021 Treatment of Parkinson's syndrome with L-dihydroxyphenylalanine (Levodopa). *Annals of Internal Medicine.* 72(1):29-35, 1970.

The effects of L-dihydroxyphenylalanine (levodopa) on symptoms of Parkinson's Syndrome was studied in 100 patients treated for a minimum of six months with 1.5grams to 8 grams per day. Sixty percent of the patients showed 50 percent or more improvement, and in some patients improvement was so marked that it was difficult to make a diagnosis of Parkinson's syndrome. Patients with severe Parkinson's syndrome or dementia showed less marked improvement. All of the major manifestations including bradykinesia, rigidity and tremor were improved to the same degree. Evidence of toxicity included nausea, anorexia, orthostatic hypotension and new adventitious movements, but there were no instances of bone marrow depression or hepatic or renal toxicity. A possible synergistic effect between anticholinergic medication and levodopa has been observed. Levodopa appears to be the most effective agent now available for the treatment of Parkinson's syndrome. 9 references. (author abstract modified)

067744 Reimer, F. Psychiatrisches Landeskrankenhaus, 7102 Weinsberg - Weissenhof, Germany /The 'disulfiram - like' action of Embran./ Uber die 'disulfiramahnliche' Wirkung von Embran. *Nervenarzt (Berlin).* 41(2):94, 1970.

Disulfiram (Antabuse) has been found to effect a number of toxic side effects, including fatalities, in alcoholic patients. For this reason, a new preparation is described which has a disulfiram-like action without the dangerous side effects. Embran is a protein and lipid free extract from skeletal musculature and is used in the promotion of coronary circulation and in liver disease. Of 17 patients treated with Embran so far, only 6 patients complained of side effects (headache, sweating, dizziness, sneezing) and 3 patients experienced vomiting, flushing, and increased blood pressure with the first swallow of beer. Further research on the extraction of Embran is planned. 5 references.

069059 Gallant, D. M.; Bishop, M. P.; Guerrero-Figueroa, R. Tulane University School of Medicine, New Orleans, Louisiana Metiapine: a new antipsychotic agent. *Current Therapeutic Research.* 12(12):794-797, 1970.

A new antipsychotic agent, a dibenzothiazepine derivative -- metiapine, is evaluated in severely chronic female schizophrenic patients. The Ss ranged in age from 40 to 53 years and had been hospitalized for approximately 20 years (average). Although no definitive conclusions can be drawn legitimately from results of an uncontrolled trial, there appears to be no doubt that metiapine is a highly active antipsychotic agent. It is, perhaps,

one of the most promising drugs encountered during 10 years of testing investigational drugs within this general patient population. The data suggest that there is a fairly wide margin between dosages which produce positive behavioral changes and those which induce significant side effects. Further controlled investigation of this compound in both chronic and acute schizophrenic patients is indicated. 1 reference. (Author abstract modified)

069070 Bobon, J.; Melon, J.; Mormont, C.; Dufrasne, M.; Pinchard A. Clinique Psychiatrique Universitaire, Rue Saint-Laurent 58, B-4000 Liege, Belgique /Long-acting neuroleptics: III. pilot study of penfluridol (R 16341)./ Neuroleptiques a longue duree d'action: III. etude pilote du penfluridol (R 16341). ***Acta Psychiatrica Belgica (Bruxelles).*** **70(4):523-551, 1970.**

A pilot study of a new long acting neuroleptic, penfluridol (R 16341), is reported. The drug, used on 20 acute psychotic patients with hallucinations, proved to be remarkably effective and without sedative or emotion related side-effects. Therefore R 16341 Janssen should be considered as a drug with essential neuroleptic effects. It has a fast action, effective in a few hours after the first administration and lasting 5 days, more or less. Results of the study indicate that a weekly dose of 40mg is sufficient, on the average. Although individual sensitivity to the drug varies widely, parkinsonian and adrenolytic side-effects are minimal. The drug does induce some easily controlled restlessness, however, the day after administration. Details of patient case histories are presented. Psychometric tests showed a clear improvement in most of the cases; and no electroencephalographic nor metabolic abnormalities were observed at any time during the investigation. It is concluded that R 16341 Janssen can be considered a strong and effective long acting neuroleptic, easy to handle and with no side-effects or toxicity. 2 references. (Journal abstract modified)

069072 Lang, W. R. Pfizer Laboratories Limited, Auckland, New Zealand Trial of a new psychotropic drug doxepin. ***New Zealand Medical Journal (Wellington).*** **72(460):184-188, 1970.**

An evaluation trial of a new psychotherapeutic agent, doxepin (Sinequan) is described. This statistically analyzed multicenter trial by 27 general practitioners, involving 160 patients with psychoneurotic illnesses in which anxiety and/or depression were prominent features, is reported. The efficacy and toleration of doxepin were determined in general practice. Results indicate that doxepin is a more than usually effective agent in the short-term treatment of psychoneurotic disorders in which anxiety and/or depression are cardinal symptoms. The present trial is presented as an example of what can be achieved by a cooperative effort of general practitioners in the evaluation of a drug at the critical stage of clinical assessment under everyday practice conditions. It is suggested that such trials may provide additional information over and above that obtainable under the restrictive conditions necessary for comparative trials. 7 references. (Author abstract modified)

08 DRUG TRIALS IN SCHIZOPHRENIA

067175 Claghorn, James; Schoolar, Joseph C. Texas Research Institute of Mental Sciences, Baylor University College of Medicine, Houston, Texas The behavioral pharmacology of oxypertine. ***Journal of Clinical Pharmacology and the Journal of New Drugs.*** **10(3):203-206, 1970.**

Oxypertine is an indole based compound with antipsychotic properties which previous studies have indicated might be especially useful in aiding psychotherapy of withdrawn schizophrenics. The effects of oxypertine and chlorpromazine in 40 schizophrenic males were compared using clinical evaluation, the Nurses Observation Scale for Inpatient Evaluation and the Brief Psychiatric Rating Scale. Effective dosage for oxypertine was established at approximately 300mg daily, and there were fewer side effects (mild manifestations of nervousness, agitation, and 1 or 2 instances of insomnia, hypotension and dryness of the mouth) reported for the oxypertine group than for the chlorpromazine group. Chlorpromazine was effective in more Brief Psychiatric Rating Scale items than oxypertine and was more of a sedative drug. 5 references. (author abstract modified)

067221 Ferholt, Julian B.; Stone, Walter N. Department of Psychiatry, Veterans Administration Hospital, 3200 Vine Street, Cincinnati, Ohio 45220 Severe delirium after abrupt withdrawal of thiothixene in a chronic schizophrenic inpatient: a case study. ***Journal of Nervous and Mental Disease.*** **150(5):400-403, 1970.**

Thiothixene (Navane), one of the thioxanthene group of antipsychotic drugs, is reported as effec-

tive in schizophrenia. Withdrawal symptoms have not been described with this group of neuroleptic drugs. A 46 year old man with a chronic schizoaffective psychosis (depressed type) was treated with thiothixene, 30mg daily for 57 days. After abrupt withdrawal of the drug he developed a severe acute brain syndrome lasting for 7 days, to which discontinuations of imipramine, benztropine, and chlordiazepoxide were temporally unrelated. At the time that thiothixene was discontinued, thioridazine (100mg b.i.d.)was substituted. This syndrome, (characterized by anxiety, agitation, disorientation, lethargy, confusion and associational looseness, visual and auditory hallucinations, garbled speech, fluctuating levels of consciousness, and delirium), was not controlled with phenothiazine but was rather quickly brought under control with reinstitution of thiothixene (10 mg t.i.d.)and stopping of all other medication. No evidence of permanent damage was found. Failure to reproduce the withdrawal syndrome in a double-blind experiment with thiothixene (10 mg t.i.d.)and placebo is attributed to possible tissue accumulation with prolonged use. 12 references. (author abstract modified)

067319 No author. Author address not given Does 'pink spot' diagnose drug? *Medical World News.* 11(42):28, 1970.

A substance identified by a positive pink spot in tests of the urine of schizophrenics, and thought by some to be a schizophrenogen, may be a normal urinary metabolite. Equivalent amounts of the metabolite 3,4-dimethoxyphenylethylamine (DMPE), the possible cause of pink spot, have been found in the urine of both schizophrenics and normals. The intensity of the phenomenon in schizophrenics may be due to metabolites of the tranquilizer chlorpromazine. If investigators used a liter of urine instead of the 100ml usually tested and carried through the assay of the pink spot, DMPE would be found in all urine, and the pink spot would be found to have many components. Two patients on high dose regimens of chlorpromazine (600mg/day to 1200 mg/day) continued to excrete pink spot material for 60 and 65 days, respectively after chlorpromazine treatment was stopped. The 3 patients who received 100mg/day to 150mg/day excreted pink spot material for 5, 5 and 7 days after discontinuance. Although the number of subjects was small, the appearance of nonappearance of a positive pink spot is apparently related in part to the presence of chlorpromazine metabolites in the urine. Also, little difference was found between the free, conjugated and total DMPE in the urine of normals and schizophrenics.

067364 Meiers, Robert L. Twin Pines Hospital, Belmont, California Lithium carbonate as an adjunct in the treatment of schizophrenia. *Schizophrenia.* 2(2-3):87-91, 1970.

In 19 cases of chronic schizophrenia lithium carbonate (usually about 250mg, 3 or 4 times a day) proved to be a valuable adjunct to the treatment program. Four case histories are presented in detail, indicating that when the schizophrenic features of the illness are controlled with mega vitamin therapy and/or phenothiazines, the manic-depressive features become more obvious and can be properly treated. 4 references.

067488 Anderson, Harvey W. Jackson Mental Health Center, 607 Highland Avenue, Tennessee 38301 A useful drug. *Journal of the Tennessee Medical Association.* 63(3):204-205, 1970.

Fluphenazine enanthate (Prolixin enanthate) has proven to be a useful i.m. injectable psychotropic agent that is long acting (the effect generally lasts one to three weeks). The drug exhibits antipsychotic properties and will tame hallucinations, reduce paranoia, decrease delusions in schizophrenic and psychotic depressive reactions, and to a lesser degree, is effective in the treatment of psychosis associated with organicity. Four case histories are provided.

067547 Ozola, M. Ya. Department of Psychiatry, Riga Medical Institute, U.S.S.R. /A therapeutical pathomorphosis of schizophrenia proceeding with paranoid disorders./ Terapevticheskiy patomorfoz shizofrenii, protekayushchey s paranoidnymi rasstroystvami. *Zhurnal Nevropatologii i Psikhiatrii imeni S.S. Korsakova (Moskva).* 70(4):600-605, 1970.

Seventy seven schizophrenic patients in the process of neuroleptic and insulin treatment (34 cases with continuous-progressive and 43 with shift-like forms of the disease) were studied. It was concluded that neuroleptic treatment does not influence the main regularities in the course of the schizophrenic process (the main type of development of the disease remains unchanged). In a continuous course, the prevalent and decisive psychopathological symptomatology (verbal hallucinosis, delusional disorders) is exclusively refrac-

tory to therapy. In a shift-like course, the neuroleptics exert a more expressed influence on psychopathological disturbances and the course of the disease; in such cases, the traits of shifts are intensified. Neuroleptic drugs in some cases elicit affective disorders in patients, which become more apparent during remissions. A comparison of insulin shock and neuroleptic treatment in paranoid schizophrenia showed a significant higher effectivity of the latter form of therapy. 34 references. (author abstract modified)

067719 Clark, Mervin L.; Huber, Wolfgang K.; Sakata, Kenneth; Fowles, Don C.; Serafetinides, Eustace A. Experimental Therapeutics Unit, Department of Medicine, University of Oklahoma Medical Center, Norman, Oklahoma Molidone in chronic schizophrenia. *Clinical Pharmacology and Therapeutics.* 11(5):680-688, 1970.

A double-blind, placebo controlled study was done to evaluate molindone (3-ethyl-6, 7-dihydro-2-methyl-5-morpholinomethylindole-4-(5H) -one hydrochloride) (MOL) as an antipsychotic agent in 37 female and 7 male chronic schizophrenic inpatients. Following a 12 week withdrawal period, the patients were given 100mg daily chlorpromazine (CPZ), which served as a standard agent for monitoring the sensitivity of the experiment, 10mg of MOL, or placebo (P), for 12 weeks, during which the daily dosage was increased to a maximum of 1000mg CPZ, 100mg MOL, or 10 P capsules by the seventh week. The overall results indicated that MOL is an active antipsychotic agent in chronic schizophrenia, effecting significant changes on several variables when compared to P. Significant CPZ, MOL group differences were demonstrable, 1 favoring CPZ and 1 favoring MOL. There were no statistically significant differences between the effect of MOL and that of P on severity of illness, manifest psychosis or personal neatness. Where drug - P differences were shown for both MOL and CPZ, the latter group appeared more impressive. Hostility measures, social interest factors and the finger tapping indices from the psychometric test battery produced differential drug affects which appeared to favor MOL. Side-effects were no more frequent than those seen with the usual psychotropic drugs. 11 references.

068450 Ban, Thomas A.; Lehmann, Heinz E. Douglas Hospital, Verdun, Montreal, P.Q., Canada Nicotinic acid in the treatment of schizophrenias. *Canadian Psychiatric Association Journal.* 15(5):499-500, 1970.

Nicotinic acid is a highly potent substance, which has a profound effect on several metabolic systems as revealed by the Canadian Mental Health Association Collaborative study which began 3× years ago. The findings to date strongly suggest that nicotinic acid or nicotinamide is not the treatment of choice for every schizophrenic patient under all possible conditions and without any further considerations. In the studies dermatological, gastrointestinal and cardiovascular reactions were commonly seen in the course of treatment. On the basis of these and other adverse effects reported, special caution is warranted if nicotinic acid is to be prescribed for patients suffering from diabetes mellitus, gout, duodenal ulcer or liver disease. In view of the controversial clinical findings and in the absence of verified indicators of therapeutic responsiveness, the practical decision as to whether nicotinic acid should be prescribed must be influenced by consideration of its known adverse effects. 2 references.

068976 Cott, Allan. 303 Lexington Avenue, New York, New York The parenteral use of vitamins in the treatment of schizophrenia. *Schizophrenia.* 2(4):177-179, 1970.

The parenteral use of vitamins in the treatment of schizophrenia, originally for patients who had suffered 1 or more relapses that had required hospitalization, then extended to initial treatment of schizophrenic patients who were responding slowly to biochemical treatment which included the use of vitamins orally, is described. Clinical response in the first category of patients was seen in most patients by the end of the second week. The second group of patients, many of who were hospitalized because of the severity of their illness, showed a more rapid clinical response than that achieved in similar patients prior to the use of parenteral vitamins. The vitamins, nicotinamide, ascorbic acid and thiamine and pryidoxine mixture, were combined in a syringe and administered by deep intramuscular injection 3 times a week. Oral use of vitamins in mega doses was continued in all patients. The clinical use of parenteral vitamins in psychiatric practice is reviewed briefly. 6 references.

069034 Kramer, Milton; Whitman, Roy M.; Baldridge, Bill J.; Ornstein, Paul H. Veterans Ad-

ministration Hospital, Cincinnati, Ohio Dream content in male schizophrenic patients. *Clinical and Basic Research.* 31(11):51-58, 1970.

Results are reported from a study to delineate the manifest dream content of schizophrenic patients and to examine the changes that occur in their dream life concomitant with successful psychotropic drug therapy. A group of male schizophrenics were monitored as to dream frequency and content both before, and after drug therapy, and the results analyzed as to patient dream recall, verbal productivity in such recall, and number of scorable dream content items in the pretreatment and posttreatment phases. The findings do not support the notion that dream reports increase with improved condition in schizophrenics. Increases in the number of scorable items, however, are consistent with clinical observations of improved communication effectiveness in such patients following remission of their symptoms. A decline in emotional dream activity was also noted. The general results tend to confirm the view that the dream life of schizophrenics is congruent with their waking behavior. 12 references.

09 DRUG TRIALS IN AFFECTIVE DISORDERS

067585 Bunney, William E., Jr.; Murphy, Dennis L.; Goodwin, Frederick K.; Borge, George F. Section on Psychiatry, Laboratory of Clinical Science, National Institute of Mental Health, Bethesda, Maryland 20014 The switch process from depression to mania: relationship to drugs which alter brain amines. *Lancet (London).* No. 7655:1022-1027, 1970.

Longitudinal behavioral, sleep, and urinary - catecholamine data are reported during 4 episodes of rapid switches from depression to mania in 3 patients. Similar sequential changes in mood and behavior occurred in each of the patients within a short time after the administration of drugs which affect brain biogenic amines (imipramine, amitryptiline, chlorapheniramine, pseudoephedrine, phenylpropranolamine, isopropromide). A brief period of normal behavior was observed immediately before the sudden onset of severe mania. Just before and during the manic period, urinary noradrenaline excretion was increased and total sleep time and rapid eye movement (REM) sleep were diminished. The evidence presented is compatible with the hypothesis that the switch process into mania may be associated with an increase in functional biogenic amines in brain, specifically noradrenaline. 24 references. (author abstract)

067591 Goodwin, Frederick K.; Brodie, H. Keith H.; Murphy, Dennis L.; Bunney, William E., Jr. Section on Psychiatry, Laboratory of Clinical Science, National Institute of Mental Health, Bethesda, Maryland 20014 Administration of a peripheral decarboxylase inhibitor with L-dopa to depressed patients. *Lancet (London).* No. 7653:908-911, 1970.

The behavioral and biological effects of L-dopa administration in combination with DL-alpha-methyl-dopa-hydrazine (MK485) were evaluated in depressed patients. Daily doses of MK485 (750 to 1000mg) and L-dopa (300 to 1500mg) were administered on a nonrandom double-blind basis to 9 depressed hospital inpatients with alternating drug and placebo periods in each patient. Three of the patients treated with the drug combination evidenced clearcut improvement, 2 of them relapsing when placebo was substituted; 6 showed no change. Those who improved were predominantly retarded. Cerebrospinal fluid homovanillic acid levels increased modestly (compared with the profound increase observed in patients on L-dopa alone) with no change in 5-hydroxy-indoleacetic acid. Plasma dopa levels in 2 patients receiving 1g of L-dopa were equivalent to levels observed in these same patients receiving 100mg of L-dopa plus MK485. The incidence of gastrointestinal side-effects was significantly lower than in patients receiving L-dopa alone. Preliminary experience suggests that alpha-methyl-dopa-hydrazine is a safe drug capable of inhibiting the peripheral decarboxylation of administered L-dopa. Consequent reduction in the incidence of peripherally based side-effects may allow more rapid attainment of therapeutic levels and a potentiation of the effects of L-dopa on the central nervous system. 36 references. (author abstract modified)

067597 Eckmann, F.; Badalik, L. State Hospital, Schleswig, Germany /Clinical study on oxypertin in chronically psychotic patients./ Klinische Untersuchungen mit Oxypertin bei chronish psychotisch Kranken. *Arzneimittel-Forschung (Aulendorf).* 20(2):268-269, 1970.

Oxypertin therapy was tried in 124 male patients with various forms of psychosis and the

results compared with observations obtained in a group of 134 similar patients not treated with the test drug. Significant therapeutic gains were achieved in the groups of involutional psychoses and schizophrenias with over 82 percent favorable results. The schizophrenic patients showed subsiding of affect and psychomotorics as well as lack of instigation; however, their hallucinatory and paranoid mode of experience still displayed dynamic elements. 1 reference. (author abstract modified)

067692 George, H. R. St. Mary Abbots Hospital, Marloes Road, Kensington, London W.8, England Two psychotic episodes associated with cannabis. *British Journal of Addiction (London).* 65(2):119-121, 1970.

A case history is presented of a 39 year old man who experienced psychotic episodes on 2 different occasions (6 years apart) which were associated with the smoking of cannabis resin. In the first occurrence, the patient experienced acute confusion following smoking of Cannabis resin. Three weeks later he was readmitted to the hospital where there was evidence of thought disorder, emotional incongruity and aural hallucinations (an acute psychotic state was diagnosed.)Treatment consisted of chlorpromazine and 5 ECT and trifluoperazine. The second occurrence also presented symptoms of confusion, followed by thought disorder, affective incongruity, and vague paranoid ideas. Chlorpromazine treatment was instituted but the acute psychotic symptoms returned when the drug was discontinued. The patient was treated with chlorpromazine and fluphenazine decanoate and became symptom free in 3 weeks. On both occasions of cannabis use the patient was under some emotional stress. 8 references.

068215 Glick, Ira D.; Hauptman, Bruce; Klein, Donald F. Research Department, Hillside Hospital, Glen Oaks, New York Pseudopregnancy, treatment of periodic psychiatric illness: a pilot study. *Psychiatric Quarterly.* 44(3):403-407, 1970.

In testing a prophylactic agent for interrupting periodic psychiatric illness in women, the use of norethynodrel with mestranol (Enovid), an agent that in high dosage produces a pseudopregnancy state, was evaluated. Four patients with periodic, psychiatric illness were treated with high doses to produce a pseudopregnant state. Relatively little modification of affective state was noted. 9 references. (Author abstract modified)

068298 Ucko, Felix A. author address not given Psychotropics in anxiety and depression -- combination or single agent. *Diseases of the Nervous System.* 31(8):539-541, 1970.

Double-blind controlled studies were made comparing a combination of amitriptyline fluphenazine with amitriptyline. Treating 87 anxious and depressed hospitalized patients, the combination drug was more effective than amitriptyline alone. More patient responses were rated excellent or good on the combination therapy (85%) than those receiving a single drug treatment (65%). In addition, significantly fewer patients receiving amitriptyline fluphenazine combination registered side effects (10 versus 21) in the study. 6 references. (Author abstract modified)

10 DRUG TRIALS IN NEUROSES

067148 Rastopchin, I. P. Orenburgskaya oblastnaya psikhiatricheskaya bol'nitsa, Orenburg, U.S.S.R. /Use of pangamic acid (vitamin B15) in cerebral artherosclerosis with mental disturbances./ Opyt primeneniya pangamovoy kisloty (vitamin B15) pri ateroskleroze sosudov mozga s psikhicheskimi narusheniyami. *Zhurnal Nevropatologii i Psikhiatrii imeni S. S. Korsakova (Moskva).* 70(2):264-267, 1970.

A clinical evaluation is presented of the effect of pangamic acid (vitamin B15) in 78 patients with asthenic, astheno-depressive, hallucinatory-paranoid syndromes and dementia due to cerebral atherosclerosis. A positive effect of pangamic acid was seen on the asthenic, astheno-depressive symptoms, irrespective of the psychopathological syndrome within which it occurred. The study demonstrated that pangamic acid is a rather potent preparation and which not only results in improvement, but in some cases, brings on an exacerbation. 8 references. (author abstract modified)

067675 Shaw, David M. M.R.C. Neuropsychiatry Unit, Carshalton, and West Park Hospital, Epsom, Surrey, England L-tryptophan in depression. *Lancet (London).* No. 7656:1111, 1970.

A critique is offered of the report (Carroll and colleagues, Lancet, May 9, 1970, p. 967) concerning the effects of treatment with L-tryptophan versus electroconvulsive therapy in cases of depression. It is suggested that, since the trial was not blind, the observers who assessed the effects of treatment by both methods were perhaps biased in their findings. The frequency of elec-

troconvulsive therapy (3 times per week) in a sequential design would almost certainly disprove the antidepressant properties of any drug. The study was terminated for each patient after treatment for only 3 weeks. This was felt to be too brief a period of time for adequate assessment. 1 reference.

067676 Coppen, Alec; Noguera, Ramon. M.R.C. Neuropsychiatric Research Unit, Carshalton, and West Park Hospital, Epsom, Surrey, England L-tryptophan in depression. *Lancet (London).* No. 7656:1111, 1970.

In reference to a previous report (Carroll and colleagues, Lancet, May 9, 1970, p. 967) of no antidepressant effect found in the use of L-tryptophan in the treatment of depression, opposing data are presented in a letter to the editor. A double-blind controlled comparison of imipramine (150 mg/day) and L-tryptophan (3 mg t.i.d.)revealed no significant difference in the therapeutic effect of these twotreatments. Three previous studies have reported the potentiation of the antidepressive effect of a monoamine -oxidase (MAO) inhibitor by tryptophan and comparative data studies show that this combination is superior to either MAO inhibition or tryptophan alone, or imipramine. 5 references.

068964 Winslow, Walter W.; Stone, Walter N.; Hofling, Charles K. Bernalillo County Mental Health Center, Albuquerque, New Mexico Drug therapy. *In: Spiegel, E., Progress in neurology and psychiatry.* New York, Grune and Stratton, 1970. 495 p. (p. 441-466).

A review of 1969 psychiatric literature on drug therapy reveals it is a useful bridge between those who view psychiatric illness from a physiological point of view and those who view it from a psychological view with resulting interdisciplinary research. Papers on drug evaluation show a trend to increase objectivity in observation and inferences, and differentiate between effects due to a given drug and effects due to other concurrent causes. Research on antipsychotic drugs including phenothiazines, butyrophenones and thioxanthenes was performed to facilitate their scientific use, particularly in neurotic conditions such as anxiety and depression. Studies were done on side-effects of experimental drugs, mood active drugs including antidepressants and lithium, tranquilizers, and stimulants and hypnotics including abuse, use of placebo, psychotomimetic drugs and drugs combined with psychotherapy. 326 references.

069025 Free, S. M.; Rudnick, A. Research and Development Division, Smith Kline and French Laboratories, Philadelphia, Pennsylvania Feasibility of evaluating psychopharmaceutical agents in cooperative studies in private practice. *Clinical and Basic Research.* 31(11):763-766, 1970.

The methodology for, and the feasibility of, conducting cooperative studies in private practice to assess antianxiety drugs, are discussed as well as the greater likelihood of such studies to better reflect the range of drug effects likely to be encountered in general experience. Specifically, 6 investigators working separately in their private practices followed an identical study plan in a cooperative effort to assess the effect of drug versus placebo treatment, under double-blind conditions, in psychoneurotic patients. Principal symptoms were anxiety, agitation, tension, and hyperactivity. Drug treatment consisted of 2mg trifluoperazine b.i.d.,for 4 to 6 weeks. A uniform Global Rating Scale and a previously tested symptom checklist (the PRL) were used to determine levels of anxiety and total morbidity before and at the end of treatment with coded medication. Results are presented for each study separately as well as for all 6 studies combined, and show that drug relieved presenting symptoms much more than placebo did and that this difference was statistically significant. 2 references. (Author abstract)

069057 Wheatley, David. General Practitioner Research Group, 325 Staines Road, Twickenham, Middlesex, England Comparative trial of a new mono-amine oxidase inhibitor in depression. *British Journal of Psychiatry (London).* 117(540):573-574, 1970.

A comparative trial of a new monoamine oxidase inhibitor (MAPI), M and B 9302, in depression is made in a double-blind procedure in which imipramine is the control drug. The trial involved 92 depressed patients. It is concluded from the results of this trial that both therapeutic effects and side-effects of M and B 9302 and imipramine were similar. Adherence to the strict dietary restrictions necessary with MAOI is an extremely difficult matter in unsupervised patients in general practice. On the results of this trial, it would not seem that M and B 9302 could be advocated generally for the treatment of depression in

general practice; although there may be specific cases where it would be justified. 6 references. (Author abstract modified)

11 DRUG TRIALS IN MISCELLANEOUS DIAGNOSTIC GROUPS

067130 Lee, Norman. 14 Davies Road, Kandos, New South Wales, 2848, Australia Studies on damage to the liver by alcohol. ***Medical Journal of Australia (Sydney).*** **2(4):203, 1970.**

In a letter to the editor, the suggestion made by Trethewie in a previous issue that patients suffering from alcohol intoxication should be treated with antihistamines is discussed. Promethazine mixed with Nicholas' 'Intravite B Group plus Ascorbic Acid' are recommended. Promethazine is indicated as the least immobilizing tranquilizer available to control withdrawal anxiety and tension. The drug alleviates the common alcoholic symptom of tender and enlarged liver. Intravite is beneficial for symptoms of delirium tremens; it helps restore thinking processes, appetite, and cardiac rhythm. The combination of promethazine with Intravite avoids vasodilatation, hypotension and syncope. Chlorpromazine is recommended for subduing a noisy or aggressive patient; mixed with Intravite it induces tranquilization or syncope. For the acutely guilt stricken or suicidal alcoholic, i.m. injection of perphenazine is suggested.

067176 De Smedt, Raoul; Rodrigus, Etienne; Debandt, Robert; Brugmans, Jo. Janssen Pharmaceutica, 2340, Beerse, Belgium Dexbenzetimide in neuroleptic-induced parkinsonism. A double-blind crossover study with a 16-week follow-up. ***Journal of Clinical Pharmacology and the Journal of New Drugs.*** **10(3):207-211, 1970.**

A double-blind crossover trial with a 16 week followup was performed to objectively assess the therapeutic efficacy, dosage, and safety of dexbenzetimide (R-16470), a new antiparkinsonian agent. The study included 16 male psychiatric patients with neuroleptic - induced extrapyramidal symptoms. The optimum dose of dexbenzetimide was a single daily oral administration of 0.75 to 1.5mg. Dexbenzetimide was significantly superior to placebo in reducing the incidence of neuroleptic induced parkinsonian symptoms; in particular, muscular rigidity was unequivocally shown to be alleviated. Blood examinations showed no evidence of toxic effects. Dexbenzetimide compared favorably with the known antiparkinsonian agents by its 24 hour duration of action and by its beneficial effect on mood and alertness. 5 references. (author abstract modified)

067512 Rosenblum, Jay A.; Shafer, Nathaniel. Department of Medicine, New York Infirmary, New York, New York Effects of diphenylhydantoin (dilantin) withdrawal on non-epileptics: preliminary report. ***Current Therapeutic Research.*** **12(1):31-33, 1970.**

Diphenylhydantoin functions as an anti-epileptic agent without the hypnotic and narcotizing effects of many other anticonvulsant drugs. It also has been used to treat various clinical syndromes not related to seizures such as Wilson's disease, diabetic neuropathy, and disturbed psychotic states. Because diphenylhydantoin (dilantin) suppresses the cerebral cortex, the question arises whether or not withdrawal from the drug will cause seizures or other withdrawal symptoms in non-epileptic patients. Hence, 49 nonepileptic patients were given diphenylhydantoin for varying periods with careful electroencephalographic monitoring. The patients experienced no adverse effects or clinical evidence of seizures or other withdrawal symptoms when the medication was precipitately withdrawn. Diphenylhydantoin has a wide margin of safety between the therapeutic level and the toxic range. 14 references.

067513 Chien, Ching-Piao; Sah, Mary; Dubiel, Gail C.; Lu, Leighmin. Early Clinical Drug Evaluation Unit, Boston State Hospital, Boston, Massachusetts Double-blind study comparing the intramuscular usage of an acridan derivative, SK and F 14336, to chlorpromazine. ***Current Therapeutic Research.*** **12(1):52-56, 1970.**

As part of a series of investigations on an acridan derivative (SK and F 14336), a clinical study on the intramuscular usage of SK and F 14336 was performed. Thirty acutely agitated patients in need of intramuscular tranquilizer medication were subjects for this study. When a patient needed an injection, he was given either high dose SK and F 14336, low dose SK and F 14336, or chlorpromazine. The results of this double-blind study generally reflected greater improvement under high dose SK and F 14336, although the trend was unspectacular. Drug -induced hypotension is dosage related in the chlorpromazine group but not in the SK and F 14336 group. Various side-effects, such as tenderness,

erythema at the injection site, control of agitation, and hypnotic affect, were displayed equally in the 3 groups. 8 references.

067569 Baldini, James T.; Neary, Edward R. Medical Department, White Laboratories, Inc., Kenilworth, New Jersey Controlled trials of an amitryptyline-fluphenazine combination in depressive neuroses and psychoses: a collaborative study. ***Current Therapeutic Research.*** **12(2):84-93, 1970.**

Psychiatric patients commonly exhibit signs and symptoms of anxiety and depression concomitantly. This is true of psychotic as well as neurotic patients and has led to the increasing use of drug combinations, consisting of a tranquilizing agent and an antidepressant agent, in treating such patients. The 6 studies described here and carried out by psychiatric investigators at 6 widely separated locations consisted of double-blind, placebo controlled evaluations of an amitryptyline-fluphenazine combination in the treatment of patients with depressive neuroses and psychosis. In these patients, depressive manifestations were generally associated with symptoms of anxiety. The drug combination in each study was significantly more effective than placebo in providing symptomatic relief, whether clinical improvement was measured by global evaluation or by decrease in severity of target symptoms. The incidence of side effects observed in patients receiving the drug combination was not significantly greater than that observed in placebo patients. 8 references. (author abstract modified)

067673 Mawson, A. B. Maudsley Hospital, London S.E.5, England Methohexitone-assisted desensitization in treatment of phobias. ***Lancet (London).*** **No. 7656:1084-1086, 1970.**

A controlled (crossover) trial was carried out to compare intravenous methohexitone sodium with the established technique of progressive muscular relaxation, with respect to their relative efficacy as reciprocal inhibitors of anxiety during treatment of a group of twelve phobic patients by systematic desensitization. Methohexitone - assisted desensitization was more than 50 percent more effective in terms of the amount of improvement produced in a small number of sessions, and was especially effective in patients with a high level of general anxiety. 14 references. (author abstract)

068955 Busse, Ewald W.; Hein, Peter L., Jr.; Erwin, C. William. Duke University Medical Center, Durham, North Carolina Electroencephalography. ***In: Spiegel, E., Progress in neurology and psychiatry.*** **New York, Grune and Stratton, 1970. 495 p. (p. 252-287).**

Four hundred and twenty six studies, consisting of books, collections of papers and journal articles, are reviewed in this chapter on electroencephalography (EEG). Improvements in EEG equipment, analysis of EEG, and use for general, physiological and experimental purposes are described. EEG was used to study slow and evoked potentials; experimental epilepsy, developmental and aging changes; cerebral death; epilepsy; neurological syndromes including narcolepsy and encephalitis; tumors; metabolic and endocrine disorders; and vascular disorders and heart disease. It was also used in drug studies on epilepsy related, psychiatric and other drugs. EEG was used in studies of psychiatric syndromes including schizophrenia, depression, autism, behavior disorders, and neuroticism. 426 references.

069060 Deutsch, M.; Saxena, B. M.; Lehmann, H. E.; Ban, T. A. Douglas Hospital, 6875 LaSalle Boulevard, Verdun, Province of Quebec, Canada Combined administration of thioridazine and fluoxymesterone in the treatment of geriatric patients. ***Current Therapeutic Research.*** **12(12):805-809, 1970.**

In a 12 week clinical study, the combined administration of thioridazine and fluoxymesterone showed significantly beneficial therapeutic effects in the treatment of geriatric inpatients. The global therapeutic effect was pronounced during the fourth week of the treatment period as shown by the brief psychiatric rating scale (BPRS). In particular, the therapeutic effect was seen on the symptoms of anxiety, hostility, suspiciousness and hallucinatory behavior (BPRS); and irritability, hostility, fatiguability, suspiciousness and anxiety (as measured by the Verdun geriatric rating scale). The range of therapeutic activity was pronounced in the symptoms related to arousal, affectivity, and perceptual disturbance. Thus, one may suggest that the combined administration of a phenothiazine, thioridazine and a hormone, fluoxymesterone, has a beneficial effect on symptoms of the arousal and affectivity parameter in geriatric patients. The therapeutic effect of the combination on the symptoms of mental integra-

tion and organicity are less pronounced. It should be noted that the combined drug administration virtually did not produce toxic and/or other adverse effects. 5 references. (Author abstract modified)

069071 Kurland, Albert A.; Goldberg, Janice B. Maryland State Department of Mental Hygiene, Baltimore, Maryland Piperacetazine (Quide) in the management of behavioral disorders in mildly retarded institutionalized boys. *Current Therapeutic Research.* 12(12):798-804, 1970.

A clinical trial of piperacetazine (Quide) was carried out over a period of 3 years on a group of 15 boys between the ages of 11 and 16 years who were displaying combinations of intellectual, emotional and social impairments of a magnitude that resulted in their being judged as 'predelinquent.'Piperacetazine significantly improved the disturbed social and emotional behaviors of the institutionalized patients within a relatively short period of time, although it did not improve cognitive functioning, at least as this was measured in the study. Piperacetazine produced no side-effects at this dosage and seemed to maintain subjects with behavior problems as well as or better than did prior medications. There was striking behavioral regression when subjects were taken off medication. 1 reference. (Author abstract modified)

12 PSYCHOTOMIMETIC EVALUATION STUDIES

067339 Grof, Stanislav. Maryland Psychiatric Research Center, Baltimore, Maryland The use of LSD in psychotherapy. *Journal of Psychedelic Drugs.* 3(1):52-62, 1970.

The effects of psycholytic therapy (the repeated administrations of 100 to 500mcg LSD within the framework of dynamic psychotherapy) on over 50 neurotic, psychotic and normal subjects were investigated. During repeated psycholytic administrations of LSD, a very dramatic improvement could be observed in the neurotics after some of the sessions. The pattern of response to LSD was in three stages: (1) recollection and reliving of early childhood traumas, paralleling Freudian psychotherapy; (2) biological rebirth drama similar to findings of Otto Rauk; and (3) deep religious and mystical experiences cast in the archetypical symbolism of Carl Jung. Between stages 1 and 2 there often occurred a crisis point which is referred to as 'ego death'. After some other sessions a marked intensification of the symptoms occurred (prolonged reactions). The most interesting phenomenon was not the quantitative oscillation of the symptoms (changes in their intensity), but a qualitative transformation (as, for example, a transformation of a depressed, suicidal homosexual into a euphoric heterosexual person but with a classical hysterical paralysis of the right hand). Treatment of psychotic patients was usually begun at a time when these subjects showed manifest psychotic symptoms. After subsequent sessions, an oscillation of the psychotic symptoms could be noticed until after a certain number of sessions, when the psychotic symptoms disappeared and the patients gained critical insight into their psychoses. Following this achievement, their development paralleled the course of therapy seen in neurotic patients, up to the point of ego death. At this point, the original psychotic symptoms, which seem to have been liquidated at the beginning of the treatment, reappeared. This time, however, they were focused on the therapist and had all the features of a real transference psychosis. The persons who received a series of psycholytic sessions, but were without serious emotional problems, underwent essentially the same development as did the neurotic patients. There were, however, 3 important differences between these 2 groups. In normal subjects the first stage was very short -- they had to relive only a few of their childhood experiences and very soon entered the realm of death and rebirth experiences. The difficult experiences were limited usually to the first hours of each session and most re-entries were positive. A very promising area for LSD administration is its use in the preparation of terminal patients for death. 15 references.

067340 Krippner, Stanley. Dream Laboratory, Maimonides Medical Center, Brooklyn, New York Psychedelic experience and the language process. *Journal of Psychedelic Drugs.* 3(1):41-51, 1970.

The effects of psychodelic experience on both receptive language (listening and reading) and expressive language (speaking and writing) was investigated. The 4 levels of psychodelic experience (sensory, recollective analytic, symbolic, and integral) provided an organizational structure in which these investigations could be explored and discussed. Psychodelic substances, when they affect language processes, sometimes appear to

assist an individual to observe the difference between the world and the object it represents. In this way, the drugs may serve as catalysts in a nonverbal training program, helping the subject translate verbal abstractions in terms of direct experience. However the subject may revert to primitive thinking, his ability to conceptualize may decrease, and he may effect a union between the word and its object, exemplified by the concretization of letters into pictures and images, by the concrescence of verbalizations with the items they represent, and by the use of words in magical ways on the part of many LSD subjects. An extremely important variable seems to be whether or not language, either receptive or expressive, becomes integrated with the ongoing psychodelic experience. At the sensory level, words are encoded and decoded in highly unusual ways. At the recollective analytic level, language often serves as a connecting system involving memory and interpretation. At the symbolic level words often become part of a mythic historic ritual. At the integral level, language rarely becomes a part of the immediate experience. However, several writers and poets have effectively transformed their religious and mystical episodes into prose and poetry. A permanent state of altered consciousness is neither practical nor desirable. However, the individual may return to the world if imprinting, conditioning, acculturation, and verbalization with new insights in his psychodelic session have been properly guided. The data obtained by responsible and imaginative investigators may indicate a way of enhancing creative functioning and lead to a better understanding of the human potential. 46 references.

067343 McGlothlin, William; Cohen, Sidney; McGlothlin, Marcella S. Department of Psychology, University of Southern California, Los Angeles, California Long lasting effects of LSD on normals. ***Journal of Psychedelic Drugs.*** **3(1):20-31, 1970.**

Personality, attitude, value, interest, and performance changes resulting from the administration of LSD to normals were studied by administering a large battery of psychological tests prior to a series of three, 200 microgram LSD sessions, and again at intervals following the third session. The test battery was organized into 4 areas: anxiety, attitude and value, esthetic sensitivity, and creativity, plus a fifth group of projective tests. The number of statistically significant differences between the experimental and control groups (controls were administered 25 micrograms LSD and 20mg amphetamine) are not grossly inconsistent with the hypothesis that they arose from chance, considering that 22 tests were administered, some of which had multiple subscales, and all tests yielded different scores. There was a significant drop in the test rate of galvanic skin response to stress situations for the experimental group at the 6 month testing period. There was some evidence of a more introspective and passive orientation accompanied by a less defensive attitude in the experimental postdrug group. The subjective reports of increase in esthetic appreciation were supported by behavioral activities, but there was no evidence of enhanced esthetic sensibility on the art tests. Similarly, there was no tendency for improvement in the postdrug measures of creativity. Persons who place strong emphasis on structure and control generally have no taste for the LSD experience and tend to respond minimally if exposed. Those who respond intensely tend to prefer a more unstructured, spontaneous, inward turning life (though not socially introverted), and score somewhat higher on tests of esthetic sensitivity and imaginativeness and tend to be less aggressive, less competitive, and less conforming. The above results should be interpreted in the context of the population from which the subjects were drawn. They were graduate students committed to a well defined goal, and were typically not motivated to take LSD, nor to alter their values or aspirations. They received the drug in a secure, esthetically pleasing setting, but without suggestions of possible lasting effect. Under these conditions, 58 percent of the experimental group subjectively reported some lasting effect after 6 months. However, attempts to measure these changes via psychological tests provided only minimal supportive data. 22 references.

067354 Smith, David E. University of California Medical Center, San Francisco, California LSD, violence and radical religious beliefs. ***Journal of Psychedelic Drugs.*** **3(1):38-40, 1970.**

The relationship between LSD and radical religious practice isbriefly described with the hope of explaining the apparent paradoxical joining of psychodelic induced violence with the avowed hippie ethic of nonviolence. The chronic use of LSD, whether the individual has a bad trip or not, can produce profound alterations in the user's psychological functioning and life style, particu-

larly if the individual lives in a psychodelic environment or community. This profound personality change is the psychodelic syndrome. A research study involving volunteers who had taken LSD an average of 65 times, demonstrated that these patients were uniquely sensitive to low intensity visual stimulation and in contrast to non-LSD using groups, there was no relationship between their evoked response to visual stimuli and their subjective response to the intensity of tactile stimuli. Chronic LSD users, particularly those involved with the psychodelic syndrome, are commonly involved in astrology, mental telepathy and ESP. They tend to be above average in intelligence, but are not athletic individuals. Conversion to a religious belief system is a psychological process which an individual defends quite rigorously and the hippies afflicted with the psychodelic syndrome are to themselves, for example, no different than 'straights' afflicted with Roman Catholicism. If LSD can alter the derivitives of man's aggressive instinct, it would follow that the drug could, depending on dosage, frequency, and type of individual, be used as a powerful therapeutic agent or as a solvent dissolving biological bonds necessary for human social organization. There is no question that LSD can facilitate the development of radical religious beliefs, and when these beliefs include blind obedience to an absolute ruler, destructive, inhuman violence can be the result. 8 references.

067355 Pahnke, Walter N.; Richards, William A. Maryland Psychiatric Research Center, Baltimore, Maryland Implications of LSD and experimental mysticism. *Journal of Psychedelic Drugs.* 3(1):92-108, 1970.

This article attempts to define, illustrate and trace the implications of a specific form of psychodelic experience that is frequently reported when a relatively high dosage of LSD is administered to normal subjects or selected mental patients in supportive settings. This form of experience is called mystical consciousness and corresponds to 9 interrelated categories used to classify traditional mystical experience: undifferentiated unity, objectivity and reality, transcendence of space and time, sense of sacredness, deeply felt positive mood, paradoxicality, transiency, alleged ineffability and positive changes in attitude and/or behavior. Other forms of drug induced altered consciousness (nonmystical) include experiences of an aesthetic, psychoanalytic, or psychotic nature. In nonmystical forms of consciousness, the empirical ego generally exists as the subject viewing objects of a visionary nature, or pondering objects of a cognitive nature; only in mystical consciousness and some psychotic reactions is the subject - object dichotomy transcended and the empirical ego extinguished. Research findings have suggested the similarity, if not the identity, between the psychodelic experience of mystical consciousness and spontaneously occurring experiences recorded in the literature of mysticism. Theological, psychiatric, and societal implications arising out of such research, stressing promise for the future as well as the very definite hazards of irresponsible experimentation, are considered. 46 references.

13 MECHANISM OF ACTION - PHYSIOLOGICAL, BIOCHEMICAL AND PHARMACOLOGICAL

067107 Faurbye, Arild. St. Hans Hospital, Department D., Roskilde, Denmark The structural and biochemical basis of movement disorders in treatment with neuroleptic drugs and in extrapyramidal diseases. *Comprehensive Psychiatry.* 11(3):205-225, 1970.

Psychiatric, neurological, and psychopharmacological aspects of movement disorders are reviewed, with emphasis on the site and mode of action of antipsychotic neuroleptic drugs in the central nervous system. The mode of action of these drugs involves transmission of the nerve impulse across the synapse; 4 transmitters have been found (dopamine, noradrenaline, serotonin, acetylcholine) which certain drugs inhibit. Other drugs, phenothiazines and butyrophenones, inhibit the receptors or interfere with amine metabolism. Movement disorders considered are parkinsonism, hypokinesia, rigidity, tremor, akinesia, choreatic and ballistic movements, and dyskinesia. Tentative conclusions about lesion sites and drug action contributory to these disorders are presented, with discussion about relevant central nuclei and pathways involved. Most cases of movement disorders produced by neuroleptic drugs are slight and reversible, but that they may be persistent and irreversible because of organic brain lesions. It must be decided if the movement disorder or the schizophrenic symptoms are the better of the two. 104 references.

067147 Panov, P. A. Voenno-meditsinskaya akademiya imeni S. M. Kirova, Leningrad, U.S.S.R. /Electroencephalographic analysis of experimental psychosis brought on by ditran./ Elektroentsefalograficheskiy analiz eksperimental'nogo psikhoza, vyzvannogo ditranom. *Zhurnal Nevropatologii i Psikhiatrii imeni S. S. Korsakova (Moskva).* 70(2):261-264, 1970.

Data is presented on the effect of ditran on the background activity of the electroencephalograph in various brain structures. It was demonstrated that the positive effect of ditran on the mean evoked potentials of the visual area of the brain during slow bioelectric activity precedes a decrease in amplitude of evoked responses. Disorders of the process of adaptation of visual evoked potentials, the incongruous amounts of response to the intensity of stimuli, an increase of variability, and an absence of correlation between the auditory and visual sites in the brain are all important links in the development of experimental psychosis. 6 references. (author abstract modified)

067602 Besser, G. M.; Butler, P. W. P.; Ratcliffe, J. G.; Rees, Lesley; Young, Pamela. The Medical Professiorial Unit and Department of Chemical Pathology, St. Bartholomew's Hospital, London, E. C. 1, England Release by amphetamine in man of growth hormone and corticosteroids: the effects of thymoxamine and propranolol. *British Journal of Pharmacology (London).* 39(1):196P-198P, 1970.

The influence of thymoxamine, an antagonist at alpha-adrenoceptors for catecholamines, and propranolol, a beta-andrenoceptor antagonist onACTH secretion was studied in twelve normal male volunteers. Thymoxamine (0.1mg/kg body weight), propranolol (0.15mg/kg body weight), or saline was administered intravenously followed by 15mg methylamphetamine 5 minutes later. Blood samples were taken at 15 minute intervals for one hour and plasma fluorogenic corticosteroids and immunoreactive growth hormone and ACTH concentrations were determined. After the placebo, methylamphetamine caused a rise in plasma corticosteroids and growth hormone. Increased ACTH levels preceded the rise in corticosteroids. This rise in plasma corticosteroids and ACTH was completely inhibited by thymoxamine, but after propranolol the maximum increase in corticosteroids was significantly greater than after placebo. The increases in concentration of plasma growth hormone were, however, significantly greater after both thymoxamine and propranolol. Thymoxamine given before intravenous insulin did not alter the rise in plasma corticosteroids and growth hormone seen in six subjects in response to induced hypoglycemic stress. Pharmacologically distinct pathways may be involved in the corticosteroid responses to methylamphetamine and hypoglycaemia, although both are thought to be mediated via hypothalamic-pituitary mechanisms. 4 references.

067623 Rao, N. S. Combined Neurological Service, Hull Royal Infirmary Effects of withdrawing dopa in Parkinson's disease. *Lancet (London).* No. 7670:470-471, 1970.

In a letter to the editor, the author describes the effects of withdrawal of dopa in 7 patients with Parkinsonism (5 men, 2 women, 60 to 67.5-yr-old) over a 1 to 4 week period. Five patients were on DL-dopa and 2 were on L-dopa. All patients were maintained on standard antiparkinsonism drugs during and after withdrawal. Patients were reexamined and objectively assessed at 2 to 4 week intervals. Improvement attributable to dopa persisted for up to 4 months after dopa was discontinued in 2 patients (one on DL-dopa and the other on L-dopa) and up to 7 months in one. In a fourth, improvement persisted for 6 weeks after discontinuance of dopa; 3 patients deteriorated over a 2 to 6 week period, but none deteriorated to their pre-dopa state. Those who were initially severely disabled improved considerably on dopa and deteriorated to or near the predopa state after withdrawal. Those who had mild or moderate disability before starting on dopa showed moderate improvement and deteriorated minimally after withdrawal. It is felt that the beneficial effect persisting several weeks afterwithdrawal of dopa is not related to plasma dopa levels but to dopamine content in the brain. While sudden withdrawal of L-dopa from patients in probably inadvisable, gradual withdrawal has no serious irreversible sequelae. 7 references.

068203 Salter, Fred J.; Pearson, Robert E. Michigan Regional Drug Information Center, University Hospital, Pharmacy Department, Ann Arbor, Michigan Doxepin HCl (Sinequan) -- current information. *Michigan Medicine.* 69(17):771-772, 1970.

Current information concerning Doxepin (Sinequan), a new dibenzoxepin derivative reputed to possess antianxiety and antidepressant activity is presented. Doxepin is well absorbed

following oral administration and is excreted primarily via the urine after metabolic transformation by the liver and kidneys. The drug is recommended for various states of anxiety or depression; studies indicate that it is at least as effective as amitriptyline. The usual starting dose is 25mg t.i.d. with an optimum dose range of 75 to 150mg per day. Contraindications include hypersensitivity, glaucoma, pregnancy and concomitant use with MAO inhibitors. Side-effects most often encountered are anticholinergic activity and drowsiness. No dependence has been reported. 15 references.

068412 Parker, William J. School of Medicine, Tufts University, Medford, Massachusetts 02155 Alcohol-drug interactions. *Journal of the American Pharmaceutical Association.* L0(12):664-665, 668-673, 677, 1970.

To make a prudent decision on the question of a possible adverse effect of combining a drug with ethyl alcohol, the pharmacist must be aware of both the pharmacology of the drugs which he dispenses and the pharmacology of ethyl alcohol. Only clinically relevant reports of interactions of drugs with alcohol are considered. Some aspects of the pharmacology of alcohol are discussed. When alcohol is taken concurrently with another drug there may be an alteration of a particular pharmacologic effect of either drug. The drugs considered are: alcohol sensitizing agents, analgesics, antianginal and antihypertensive drugs, anticoagulants, antihistamines, antidepressants, antiinfective agents, antipsychotic tranquilizers, hypoglycemic agents, narcotics, sedatives, hypnotic drugs and centrally acting muscle relaxants. A table summary of significant alcohol and drug reactions is included. It is felt that the pharmacist must be totally committed to providing both the patient and the physician with service as well as products. They have a responsibility to try to detect and prevent drug interactions. 76 references.

068414 Reynolds, E. H.; Preece, J. M.; Bailey, J.; Coppen, Alec. National Hospital for Nervous Diseases, Queen Square, London, W. C. 1, England Folate deficiency in depressive illness. *British Journal of Psychiatry (London).* 117:287-292, 1970.

The relationship of low serum folate concentrations to the severity of depressive illness and to variables such as diet and drugs, which could influence serum folate, are investigated. Serum folate and vitamin B12 levels have been measured in 101 patients with depressive illness. Subnormal folate levels (2.5nanograms/ml. or less) were found in 24% and subnormal vitamin B12 levels (150picograms/ml. or less) in 2.2% of patients. Thirteen patients (14.4%) had low vitamin B12 levels (200pg./ml. or less). Patients with subnormal folate levels were found to have significantly higher depressive scores, and significantly lower validity scores on the Marke-Nyman temperament scale, both on admission and on discharge. Subnormal folate levels could be a consequence of dietary deficiency or could possibly be causal of depression through interference with tyrosine or tryptophan hydroxylation. 20 references. (Author abstract modified)

068975 Altschule, Mark D.; Hegedus, Zoltan L. Harvard Medical School, Boston, Massachusetts Some relations between indoles and psychiatry. *Schizophrenia.* 2(4):166-176, 1970.

Some relations between indoles and psychiatry are considered with respect to the clinical phenomenon of mental disorder produced by the ingestion of certain indoles. Review of the literature suggests that there is good reason to study the possible roles of indoles in clinical syndromes of brain dysfunction. While other chemical compounds have hallucinogenic action, also, the hallucinogenic indoles, including lysergic acid, dimethyltryptamine and its derivatives, bufotenine and psilocybin, adrenochrome, harmine, yohimbine and reserpine, are discussed here. Hallucinogenic indoles are formed by a number of plant and animal species. Their role in metabolism is unknown but the occurrence of these indoles in many biologic organisms raises the possibility of their synthesis in the tissues of man. Recent metabolic studies show that the indole pathway of epinephrine metabolism is available in humans. The pathway comprises products and processes that are toxic to brain and to blood cells. It is believed to be evident that in humans epinephrine has 2 available pathways of degradation: 1) the 3-methoxy-4-hydroxymandelic acid pathway, and the 2) indole pathway. The first ordinarily predominates. The factors that might lead to the dominance of the second have been studied incompletely. Metabolic schemes and a method for measuring bisulfite susceptibility of red blood cells are presented, as is the results of application of the bisulfite test to the blood of normal and psychotic individuals. 42 references. (Author abstract modified)

069051 Lemberger, Louis; Silberstein, Stephen D.; Axelrod, Julius: Kopin, Irwin J. Laboratory of Clinical Science, National Institute of Mental Health, Bethesda, Maryland 20014 Marihuana: studies on the disposition and metabolism of delta-9-tetrahydrocannabinol in man. *Science.* 170(3964):1320-1322, 1970.

Delta 9-tetrahydrocannabinol (the major active component of marihuana) administered intravenously to normal human volunteers persists in plasma for more than 3 days (half-life - 56 hours). Its metabolites appear in plasma within 10 minutes after administration and persist along with the precursor compound. Delta 9-tetrahydrocannabinol is completely metabolized in man, and the radioactive metabolites are excreted in the urine and feces for more than 8 days. 17 references. (Author abstract)

069053 Martin, W. R.; Sloan, J. W. National Institute of Mental Health, Addiction Research Center, P. O. Box 2000, Lexington, Kentucky 40501 Effects of infused tryptamine in man. *Psychopharmacologia (Berlin).* 18(3):231-237, 1970.

Tryptamine, infused intravenously in man, facilitates the patellar reflex, dilates pupils and elevates blood pressure. It also causes changes in vision and hearing, as well as nausea, vomiting, dizziness, sweating and heaviness of body. These changes are similar to those produced bylysergic acid diethylamine (LSD) - like hallucinogens and are consistent with the hypothesis that LSD - like hallucinogens interact with tryptamine receptors as one mode of action. 12 references. (Author abstract)

069081 Curzon, G.; Bridges, P. K. Department of Chemical Pathology, Institute of Neurology, Queen Square, London, England Tryptophan metabolism in depression. *Journal of Neurology, Neurosurgery and Psychiatry (London).* 33(5):698-704, 1970.

Tryptophan metabolism is studied in psychiatric patients suffering from endogenous depression. Oral loads of L-tryptophan were given to patients with endogenous depression and to a control group without this condition. Urinary excretion was determined of the tryptophan metabolites on the pyrrolase pathway: kynurenine, 3-hydroxykynurenine, and 3-hydroxyanthranilic acid. Female endogenously depressed subjects excreted significantly more kynurenine and 3-hydroxykynurenine but not the subsequent metabolite 3-hydroxyanthranilic acid than did female control subjects. Variability of excretion of kynurenine and 3-hydroxykynurenine at different times by the same subject was much greater in the endogenously depressed than in the control group. There was no consistent temporal relationship between excretion of metabolites and severity of the depressive illness. The possible significance of the findings in relation to defective tryptophan metabolism in the brain in endogeous depression is commented upon. 42 references. (Author abstract modified)

069082 Markovic, Vjerica; Rolovic, Zoran; Moric-Petrovic, Slavka; Ruvidic, Rajko; Nikolic, Julijana. Laboratorija za humanu citogenetiku, Zavod za mentalno zdravlje u Beogradu, Belgrade, Yugoslavia. /Analysis of chromosomes bbefore and after treatment with Imuran./ Ispitivanje hromosoma pre i posle lecenja imuranom. *Anali Zavoda Za Mentalno Zdvavlje (Beograd).* 2(2):105-113, 1970.

Results are presented of a study to detect chromosome changes in patients suffering from systemic lupus erythematodes. Small doses of the drug were given to 5 female patients with systemic lupus erythematodes, and one female patient with idiopathic thrombocytopenic purpura suspected to lupus. The analyses made before the treatment revealed that the patients with systemic lupus had no specific changes on the chromosomes of peripheral blood cells and of the bone marrow cells which could be detected. A satellite was found on the chromosome 18 of the female patient with idiopathic thrombocytopenic purpura, but it was felt that it has no relation with the illness nor with the administration of Imuran. After the administration of the relatively small total doses of Imuran, no changes were found on the chromosomes in the peripheral blood cells. Further examination will be directed towards the effect of Imuran on the bone marrow cells and the effect of high total doses of Imuran on both tissues: peripheral blood and bone marrow cells. 16 references. (Journal abstract modified)

069085 Nikolic, Branka; Barjaktarovic-Nikolic, Kosara. author address not given Morfolep in treatment of some forms of epilepsy./ Morfolep u terapiji nekih formi epilepsije. *Anali Zavoda za Mentalno Zdravlje (Beograd).* 2(2):87-93, 1970.

The use of Morfolep therapy in treating some forms of epilepsy is discussed, based on case study results. It is stressed that the chemical formula is somewhat different from the succinimidin

preparations, and that which we had at our disposal up to the present. The administration of Morfolep in some lighter cases of petit mal epileptic seizures or in some combined forms of epilepsy gave good results. The period of observation was sufficiently long to ascertain its efficiency in cases of electroclinically verified petit mal and its variations, as well as in 2 cases of combined temporal and grand mal epilepsy. From 20 cases treated with Morfolep, in 5 patients no more seizures occurred, and in 10 cases a considerable improvement was noticed, a result that is considered excellent because the forms of epilepsy were rather severe and were resistent to previously applied therapy. Side-effects such as persistent vomiting occurred in 2 patients, so that the administration of the drug was stopped at once. Considering the great number of population with epilepsy, and especially with combined and more severe forms of epileptic seizures, with the introduction of Morfolep in the therapy, the number of available antiepileptic drugs, and with that the possibilities of therapeutical combinations are increased. 8 references. (Journal abstract modified)

069515 Dettbarn, W.-D.; Heilbronn, E.; Hubbard, B. Department of Pharmacology, Medical School, Vanderbilt University, Nashville, Tennessee The effect of a psychotomimetic glycolate and its antidote eserine on the ACh content of the lobster walking leg nerve. *Life Sciences (Oxford).* 9(24):1409-1415, 1970.

The effect of a psychotomimetic glycolate and its antidote eserine on the ACh content of the lobster walking leg nerve is studied. Experiment results show that the glycolate significantly reduces the amount of acetylcholine found in the lobster nerve fibers. The effect is pronounced in the absence of the cholinesterase inhibitor eserine and counteracted by the presence of the latter compound. Eserine itself increased the tissue concentrations of ACh. Synthesis of ACh was slightly impaired by high concentrations of the glycolate, probably because of beginning general poisoning of the tissue. Lower concentrations of the glycolate on the contrary stimulate acetylcholine systhesis, an observation that suggests that the synthesis may be triggered by low concentrations of ACh within the tissues. A plausible interpretation of the findings might be that the low concentrations of ACh found in the tissue in the presence of the glycolate are due to increased release of ACh in the presence of the drug, followed by cholinesterase catalyzed hydrolysis of ACh. 19 references.

14 MECHANISM OF ACTION - BEHAVIORAL

067264 Shapiro, Arthur K. Author address not given /The use of haloperidol for Gilles de la Tourette's syndrome./ Discussion. *New York State Journal of Medicine.* 70(17):2214, 1970.

The discussion following the presentation of reports on Gilles de la Tourette's syndrome, appearing in the New York State Journal of Medicine, September 1970, made the following points: haloperidol was the best and most predictable treatment; it should be given early in the illness to prevent secondary severe psychologic consequences; initial dosages should be low (0.5mg, 4 times daily); and dosage should be increased rapidly until maximum alleviation of symptoms is achieved (average daily dosage being 15mg) or side-effects commence. The syndrome was caused by a neurophysiologic impairment of the central nervous system.

067265 Shapiro, Arthur K. 525 East 68th Street, New York, New York 10021 Dangers of premature psychologic diagnosis. *New York State Journal of Medicine.* 70(17):2210-2213, 1970.

A 46-year-old male patient with a 33 year history of Gilles de la Tourette's syndrome, who was successfully treated with haloperidol, is presented to illustrate the misleading and harmful consequences of attributing a psychologic cause to a disease of unknown origin. Psychologic tests done on the patient at age 30 and 43, and psychiatric reports at age 43 and 46, describe the patient as having chronic psychoneurosis, obsessive-compulsive type, in association with Tourette's syndrome. Prognosis was that without treatment, the symptoms would progress and that he would become a withdrawn schizophrenic. Despite increased symptoms and hardship, the patient did not become the withdrawn schizophrenic predicted 16 years earlier. Treatment with haloperidol was successful, all symptoms disappearing except for an infrequent facial tic, and the patient's ego functioning, capacity, and development markedly improved after control of the symptoms. 15 references.

067739 Leder, Alfred. Psychologisches Institut der Universitat, Zurichbergstrasse 43, CH-8044 Zurich,

Switzerland /Tegretal: the problem of psychotropic action./ Tegretal: Zum Problem der psychotropen Wirkung. ***Nervenarzt (Berlin).*** **41(2):59-67, 1970.**

The efficacy of Tegretal, (5-carbamyl-5H-dibenzo (b,f) azepin, in the treatment of epilepsy is evaluated. One third of the patients treated for 3 months with Tegretal showed improvement in the psychological testing, and differences were significant at the 5% level in 4 of the 10 diagnostic procedures. The Tegretal treated patients were evaluated as more productive and more alert, with a diminution in somatic complaints when compared to the control subjects. Tegretal is also effective in the amelioration of sleep patterns, and in self-maintenance and social participation. The patients seem less disturbed with respect to their seizures and hypochondriacal symptoms. The drug is well tolerated. 70 references. (author abstract modified)

067862 Brown, William T. Department of Psychiatry, University of British Columbia, Vancouver 8, British Columbia, Canada A comparative study of three hypnotics: methyprylon, glutethimide and chloral hydrate. ***Canadian Medical Association Journal (Toronto).*** **102(5):510-511, 1970.**

A controlled study designed to test the hypnotic potential of methyprylon, glutethimide and chloral hydrate was performed on 50 patients with long-term insomnia. Placebo reactors were excluded from the experiment before initiation of the main trials. No significant differences in effectiveness in maintaining sleep could be found between the drugs. Methyprylon was found to be the fastest agent in sleep induction. No untoward reactions were reported with any of the drugs.

067864 Davison, K.; Duffy, J. P.; Osselton, J.W. Newcastle General Hospital, Westgate Road, Newcastle-upon-Tyne, NE4, 6BE, England A comparison of sleep patterns in natural and mandrax- and tuinal -induced sleep. ***Canadian Medical Association Journal (Toronto).*** **102(5):506-508, 1970.**

A comparison of the effects of Mandrax and Tuinal on overnight sleep in 14 normal subjects is reported. The subjects were healthy students and staff volunteers. Recording of REM's and EEG was done using silver disc electrodes and the records were assessed for significant differences between the time spent in each sleep phase: natural sleep vs Mandrax-induced sleep and natural sleep vs Tuinal-induced sleep. Mandrax-induced sleep was found to be significantly longer in duration than natural sleep. Tuinal produced a reduction in the REM phase of sleep, although no statistical differences in sleep phases or total sleep duration was noted between the two drugs. 8 references.

067924 Lewis, S. A.; Oswald, I.; Evans, J. I.; Akindele, M. O.; Tompsett, S. L. University Department of Psychiatry, Royal Edinburgh Hospital, Morningside Park, Edinburgh EH10 5HF, England Heroin and human sleep. ***Electroencephalography and Clinical Neurophysiology (Amsterdam).*** **28(4):374-381, 1970.**

Four normal males had a subcutaneous injection of 7.5mg heroin on 3 successive nights. During this period the percentage of REM sleep was decreased with respect to baseline values for these subjects and showed a trend back to control values over the 3 nights. On withdrawal there was a moderate but immediate percentage of REM sleep increase which, over the first 3 hr of sleep, was significant. Two of the above subjects received an additional 7 injections of 7.5mg heroin 2 months after the previous ones. Again the proportion of REM sleep was reduced in both subjects and there was the trend back to baseline values over the 7 nights. One subject had increased REM sleep immediately on withdrawal. Evidence of withdrawal was apparent for some 2 months after stopping heroin. Other evidence of withdrawal was seen in the decreased delay to the first REM period (less than 45 min) and in the increased amount of REM sleep in the first 2 hr of sleep greater than 35 min). The other subject showed little evidence of withdrawal effects in sleep. In both experiments, heroin administration, rather than giving an undisturbed sleep, resulted in an increased frequency of shifts to stage 1 sleep (drowsiness) or wakefulness and an increased delay to the onset of the first stage 2 of the night. 24 references. (author abstract modified)

068005 Malpas, Ann; Rowan, A. J.; Joyce, C. R. B.; Scott, D. F. Department of Pharmacology and Therapeutics, London Hospital Medical College, London E.1, England Persistent behavioural and electroencephalographic changes after single doses of nitrazepam and amylobarbitone sodium. ***British Medical Journal (London).*** **No. 5712:762-764, 1970.**

In a double-blind crossover trial, the effects of amylobarbitone sodium (100mg and 200mg), nitrazepam (5mg and 10mg), and placebo on task

performance were tested in normal healthy young people. Each subject took the test drugs as pills orally before retiring for the night. Subjective sleep questionnaires, subjective mood ratings, card sorting tests of motor acuity and decision time, and electroencephalogram (EEG) readings were taken on the following day. Subjects reported no hangover effects, and rated themselves as having had a better and longer night's sleep after high doses of both drugs than after placebo. There were no differences between drugs and placebo with respect to feelings of 'good mood' or 'tension'; subjects rated themselves as 'alert' more often after drug than after placebo. Motor performance after nitrazepam was slower than after placebo; amylobarbitone sodium did not affect motor performance. Decision time was significantly slowed both after treatment with nitrazepam and after amylobarbitone sodium. EEG recordings showed more drowsiness and light sleep after treatment with nitrazepam than after amylobarbitone or placebo. The results show that some slowing of performance is detectable for at least 12 hours after a normal healthy subject has taken a hypnotic dose of either amylobarbitone sodium or nitrazepam. 17 references.

068021 No author. Author address not given To sleep, perchance to dream: new drug for insomniacs doesn't interfere with REM time. ***Medical World News.*** **11(24):20, 1970.**

Flurazepam hydrochloride (Dalmane), a hypnotic which is related to chlordiazepoxide (Librium) and diazepam (Valium) has just been released after 6 years of clinical trials by Roche Laboratories. Dalmane was the first hypnotic to come to the market after evaluation in sleep laboratories utilizing objective physiological measurements rather than subjective response. Tested in 53 double-blind studies of more than 2000 patients, as well as in other studies, its high level of effectiveness and safety has been confirmed. The recommended adult dose of 30mg induces sleep in 22 minutes. A significant features is that the compound does not cut short REM sleep. Dalmane cut down stage 4 sleep and high doses produced daytime drowsiness. In a study of 19 insomniacs, one night was spent without psychotropic drugs; the patients were then given Dalmane or a placebo for 7 consecutive nights. In no case did the Dalmane fail to induce effective sleep. The principle investigator was Dr. Anthony Kales.

15 TOXICOLOGY AND SIDE EFFECTS

067138 McKnelly, W. V., Jr.; Tupin, Joe P.; Dunn, Marvin. University of Kansas Medical Center, Kansas City, Kansas Lithium in hazardous circumstances with one case of lithium toxicity. ***Comprehensive Psychiatry.*** **11(3):279-286, 1970.**

Four case reports presented demonstrate that lithium carbonate can be used in the treatment of manic episodes in spite of severe or potentially severe physical conditions if there is careful monitoring of the lithium, close clinical observation for lithium toxicity, and careful control of the medical illnesses. In these 4 patients (33 to 68 years old), the predominant complication was cardiac or circulatory disease or both, and in 1 case, polycystic kidneys. All 4 were successfully treated with lithium carbonate, due to careful monitoring and collaboration of the various clinical specialties involved. It is felt that the personal, social, or physical complications of recurrence may counterbalance the controlled risk of lithium in such cases. 12 references.p

067174 Lampe, William T., II. Brockie Medical Center, York, Pennsylvania 17403 Adverse effects with clomacran. ***Journal of Clinical Pharmacology and the Journal of New Drugs.*** **10(3):171-174, 1970.**

A study is reported of the toxic side effects of clomacran, a drug used in the treatment of schizophrenic patients. In 11 of 44 patients treated with clomacran, a new neuroleptic structurally related to the phenothiazines, toxic side effects were seen which included pigment deposits in the lens of the eye (2 patients), neutropenia (1 patient), and liver function abnormalities (8 patients). The liver function abnormalities and neutropenia were reversible. The neutropenia with associated severe eosinophilia was reproduced on reexposure to clomacran. Nine months after stopping clomacran, one patient had persistent pigment deposits in the lenses of both eyes. Epileptic seizures and photosensitivity have been noted by other observers. It is suggested that patients under study with clomacran be carefully observed with periodic white blood cell counts, slit lamp examination of the lens and liver function studies. The toxic side effects associated with clomacran are serious and may outweigh the therapeutic value of the drug. 13 references. (author abstract modified)

067213 Voltolina, Eugene J. Medical Corps, U. S. Navy, Neuropsychiatric Service, Naval Hospital, Oakland, California Spinal fluid creatine phosphokinase abnormalities following LSD usage. ***Clinical Toxicology.*** **3(1):85-87, 1970.**

An investigation was made of creatine phosphokinase (CPK) in cerebrospinal fluid (CSF) of patients (19 to 26 years of age) who had used LSD to study its potential for causing brain damage. Five LSD users and six control subjects were tested and CSF pressures, protein, cell count, serology and chloride were also measured. Marked elevations were found in LSD users, while none appeared in CSF of the control group. The time relationship between the last dose and time of measurement showed an inverse relation of CPK levels with time elapsed since LSD usage. If CPK levels represent an association with brain damage, it can be concluded that LSD may cause brain damage. However, since CPK level falls as a function of time elapsed since LSD exposure, the damage may be transient. 2 references.

067218 Smith, David E.; Fischer, Charles M. Haight-Ashbury Medical Center, San Francisco, California An analysis of 310 cases of acute high-dose methamphetamine toxicity in Haight-Ashbury. ***Clinical Toxicology.*** **3(1):117-124, 1970.**

Three hundred ten cases of methamphetamine toxicity were studied to provide a better understanding of this new major drug abuse problem. Methamphetamine is a potent sympathomimetic amine which produces motor activity, tremors, sleeplessness and large increases in blood pressure. The physical effects are variable and dependent on dose, duration of use and mental state of the individual user. The human lethal dose is likewise variable due to development of tolerance. Aside from general debility and malnutrition arising from chronic use, the main associated problem is hepatitis caused by an unsanitary environment. Prolonged high doses may also have a direct effect on the liver. The acute psychiatric problems are divisible into four categories: the acute anxiety reaction, psychotic reaction, exhaustion and the withdrawal reaction. The authors feel that the primary determinants of whether a patient undergoes a psychotic or an anxiety reaction to methamphetamine are the immediate social environment of the user, and the extent of his experience with amphetamines. 12 references.

067288 Knowles, M.; Saunders, M.; McClelland, H. A. Demyelinating Diseases Unit, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne, NE 4 6BE, England The effects of phenothiazine therapy on lymphocyte transformation in schizophrenia. ***Acta Psychiatrica Scandinavica (Kobenhavn).*** **46(1):64-70, 1970.**

Lymphocyte stimulation with phytohemagglutinin-M (PHA-M) was studied in 9 phenothiazine treated and 4 untreated schizophrenics and compared with the response of 11 normal individuals. No significant difference was found between untreated schizophrenics and normals, but schizophrenics on prolonged phenothiazine therapy showed a significantly impaired response to PHA-M. The addition of phenothiazine perphenazine to lymphocytes in culture produced a concentration dependent impairment of transformation. The viability of lymphocytes from treated schizophrenics was found to be reduced compared with normals. Thus, lymphocyte abnormalities in schizophrenia may be drug induced; there is no primacy lymphocyte disorder. 12 references. (author abstract modified)

067341 Shick, J. Fred E.; Smith, David E. University of Chicago, Chicago, Illinois Analysis of the LSD flashback. ***Journal of Psychedelic Drugs.*** **3(1):13-19, 1970.**

A detailed clinical analysis of the flashback associated with LSD, and therapeutic guidelines for the physician who may have a patient in distress from such a recurrence, are presented. A flashback is a transient spontaneous recurrence, usually multiple, of certain aspects of the psychodelic drug experience occurring after a period of relative normalcy following the original intoxication, and should be distinguished from prolonged psychotic and nonpsychotic reactions to the psychodelic drugs. The prolonged reactions are continuous with the intoxication itself and may not be recognized until days after when the patient complains he has continued to experience unusual feelings or ideas without relief since the intoxication. These may be psychotic or nonpsychotic depressions, schizophreniform reactions, acute paranoid states, or chronic anxiety reactions, but are more or less typical psychopathological entities. The bad trip is confined to the time period of the intoxication (8 to 18 hours) and is usually an acute anxiety or panic state, sometimes with paranoid components and may progress to a prolonged reaction or be as-

sociated with flashbacks of the experience later on, particularly if managed incorrectly. The flashback, primarily psychological rather than chemical in nature, may be related to traumatic events within the LSD intoxication itself. They are seen frequently after bad trips, many of which have been treated in a hospital setting, and although the bad trip appears to have etiological significance, its exact relationship with the flashback has not been explored. The flashback not limited to LSD can be seen after a variety of psychodelic drugs including DOM (STP) and DMT. Varying types of LSD flashbacks include the perceptual, somatic and emotional flashbacks, of which the latter two are far more distressing to the patient. Flashbacks occur frequently but not exclusively with chronic use, and may occur after a single intoxication. In treatment the patient is reassured that the flashback phenomena do not represent permanent brain damage. Abstinence from psychoactive drugs, particularly the psychodelics, is recommended. If any drugs are used at all in an attempt to control anxiety, minor tranquilizers (Librium, Valium or phenobarbital) are preferred (the major tranquilizers often make flashbacks worse). 21 references.

067342 Egozcue, Jose; Irwin, Samuel. Instituto de Investigaciones Citologicas de la Caja de Ahorros y M.P. de Valencia, Valencia, Spain LSD-25 effects on chromosomes: a review. ***Journal of Psychedelic Drugs.*** **3(1):10-12, 1970.**

A brief review of the major and more recent developments concerning the genetic effects of LSD is presented. Chromosomal damage to human leukocytes in vitro and in vivo following administration of LSD-25 has been demonstrated. Hereditary syndromes exhibiting such increasedchromosomal aberrations have been correlated with an increased incidence of cancer and leukemia. The presence of chromosomal aberrations in LSD users is still in dispute. The possibility that LSD might produce congenital malformations was raised not only by the presence of chromosomal breaks in users of the drug, but by the presence of chromosomal aberrations in some children exposed to the drug in utero and by reports of malformations induced by LSD in experimental animals. The weight of evidence suggests that LSD can and does produce chromosomal aberrations in circulating blood cells, but probably not in bone marrow. Without corresponding alterations in the bone marrow, chromosomal changes in circulating leukocytes are unlikely to have serious medicalconsequences. Studies of LSD's effect on germinal cells have been conducted only in experimental animals, and the results are far from conclusive. While stunted growth and a number of malformations in mice, rats and hamsters have been produced, negative results have also been reported. No one to date has conclusively proven that any birth defect is directly attributable to parental use of LSD. Even if a chemical causes no gross chromosome abnormalities, it may still produce gene or point mutations in the chromosomes of somatic or germinal cells. The production of these phenomena by LSD remains to be demonstrated. An unusually high incidence of spontaneous abortions, miscarriages or stillbirths among pregnant LSD users could be evidence of such mutations. It may also be related to the uterine-specific actions of lysergic acid and its derivatives. 33 references.

067510 Holden, J. M. C.; Estrada, T.; Wood, M. J. Department of Psychiatry, Missouri Institute of Psychiatry, University of Missouri School of Medicine, St. Louis, Missouri 63139 Butaperazine and hemoglobin C trait. ***Current Therapeutic Research.*** **12(1):57-63, 1970.**

A case of an apparent association between psychotropic drug treatment and the incidence of peripheral blood target cells in a patient with hemoglobin C trait is reported. The patient was a 38 -year-old male Negro with a history of auditory hallucinations and paranoid delusions. After treatment with chlorpromazine and subsequent remission of symptoms, the patient was discharged only to be readmitted a year later with similar complaints. He was then maintained on butapherazine. As butaperazine dosage was increased the incidence of target cells increased to the level of 80% of total red cell count. After routine hematological screening, hemoglobin electrophoresis showed 68% hemoglobin A and 32% hemoglobin C which, together with the finding of impaired fragility, lead to a diagnosis of hemoglobin C trait. A blind experiment was undertaken to determine the relationship, if any, to butaperazine therapy. It was decided that the changes in the incidence of target cells in the peripheral blood was mechanical in nature and not a contraindication to psychotropic drug therapy. A discussion of the nature of psychotropic drug effects on cellular morphology and function is given. 19 references.

067570 Krumholz, W. V.; Sheppard, C.; Merlis, S. Research Division and Clinical Facilities, Central Islip State Hospital, Central Islip, New York Menstruation changes as unusual side effect in a molindone trial. *Current Therapeutic Research.* 12(2):94-96, 1970.

Molindone is an oxygenated indole derivative with a chemical structure distinctly different from that of the phenothiazines. Its sedative - tranquilizing effects as reported in the literature are mentioned. This communication deals with a hitherto unreported side effect with this agent. Ten women with chronic mental illness treated with Molindone in doses of 25 to 125 mg. daily during a six week period exhibited no clinical improvement. In addition to exhibiting a variety of side effects, 5 to 10 women demonstrated menstrual irregularities which did not exist prior to this treatment. There is presumptive evidence to suggest a causal relationship of the menstrual irregularities to the administration of Molindone. 4 references.

067657 Hunder, K. R.; Boakes, A. J.; Laurence, D. R.; Stern, G. M. Clinical Pharmacology Section, Medical Unit, University College Hospital Medical School, London, W.C.I, England Monoamine oxidase inhibitors and L-dopa. *British Medical Journal (London).* No. 5719:388, 1970.

Recent reports that monoamine oxidase (MAO) inhibitors potentiate the pressor effect of L-dopa in parkinsonian therapy are discussed interms of a case history. The parkinsonian patient had previously been treated with imipramine (25mg, t.i.d.)and benzhexol (5mg, t.i.d.), which was changed to phenelzine (15mg, t.i.d.)after admission. The effect of 50mg L-dopa on blood pressure showed an increase of the systolic pressure from 140mm Hg to 180mm Hg after injection. Three weeks after discontinuance of the MAO inhibitor, doses of L-dopa up to 500mg produced no blood pressure change. Alpha-adrenergic blocking drugs control the hypertension. This study indicates that combination therapy with amine precursors and MAO inhibitors may dangerously depress some patients. At least 1 month is recommended for discontinuance of MAO-inhibitor therapy prior to L-dopa administration, but imipramine or amitriptyline appear to be safe if antidepressive therapy is also needed. 9 references.

067743 Manz, F. Neurologische Klinik, 78 Freiburg i. Br., Hansastr. 9, Germany /Neurotoxic side effects in disulfiram (Antabuse) overdosage./ Neurotoxische Nebenwirkungen bei Disulfiram (Antabus)-Uberdosierung. *Nervenarzt (Berlin).* 41(2):92-94, 1970.

The administration of disulfiram (Antabuse) can, in certain cases, act as supportive therapy together with psychotherapy and sociotherapy in alcoholic patients. By producing an alcohol sensitization, Antabuse decreases the craving for and continued drinking of alcohol, but the pharmacology of this drug must be considered before administration. Alcoholics with psychoorganic degeneration, epilepsy, extensive liver damage, coronary insufficiency, and psychoses in their history are to be excluded from this therapy. The patient and his family should be forewarned, and signs of symptomatic psychoses and neurological disorders must be looked for. The aim of the medication is to help the alcoholic over a difficult period in order to achieve the final goal of complete abstinence. 32 references. (author abstract modified)

067836 Hindle, W.; Posner, E.; Sweetnam, M. T.; Tan, R. S. H. General Hospital, Poole, Dorset, England Pleural effusion and fibrosis during treatment with methysergide. *British Medical Journal (London).* No. 5696:605-606, 1970.

Two patients being treated for migraine with methysergide developed extensive pleural fibrosis, and in addition one of them had bilateral pleural effusions. After treatment was stopped, these complications which are thought to be drug induced, cleared in the next few months. A causal relationship between methysergide treatment and otherwise unexplained fibrosis has now been widely accepted. In conditions as common as pleural effusions and fibrosis the diagnosis of drug induced disease is more difficult to prove and rests mostly on circumstantial evidence. The most striking feature in these cases was the degree of radiological clearing of pleural fibrosis after cessation of methysergide therapy. This is an uncommon occurrence in pleurisies of other origins, but in accordance with the regression observed in retroperitoneal fibrosis due to methysergide. 7 references. (author abstract modified)

067868 No author. Author address not given /LSD condemned as treatment agent./ L.S.D. in psychiatry. *Lancet (London).* No. 7682:1091, 1970.

A letter to the editor describes the disastrous results of LSD therapy. Anxiety and depression

brought on by social and family problems led the patient to seek psychiatric treatment at a London hospital. She was given weekly doses of LSD by her psychiatrist, who assured her that the drug would do her no positive harm. However, the patient experienced acute panic reactions at each administration of LSD, and eventually began to experience spontaneous reactions out of the hospital. To quell the panic of the spontaneous reactions, she was given barbiturates, to which she became addicted. At present, the patient continues to experience occasional spontaneous reactions (although her LSD therapy has concluded.), and she has long periods of depression and near despair. She feels that LSD nearly brought her to psychosis.

067900 Demers, Robert; Lukesh, Robert; Prichard, James. Departments of Psychiatry and Neurology, Yale University School of Medicine, New Haven, Connecticut Convulsion during lithium therapy. ***Lancet (London).*** **2(7667):315-316, 1970.**

In a letter, the authors note the case of a 22 year old woman who suffered a grand mal seizure, with loss of consciousness, tonic-clonic movements, tongue biting, and urinary incontinence 4 days after being started on lithium carbonate (300mg) for control of mania. Her morning serum lithium level after 2 days treatment was 0.75mEq/liter and on the day of seizure it was 0.78mEq/liter. Before lithium treatment, hepatic and renal function and serum electrolytes (except for calcium, 8.8mg/100ml) were normal. There was no trace of barbiturates or chlordiazepoxide in the serum 4 days before the seizure. After the seizure, neurological and laboratory examination were normal except for calcium which was 8.3mg/100ml. Spinal puncture and head and chest x-rays were normal. An EEG done 6 days after the seizure showed abnormalities compatible with the lithium effect. The patient had a history of childhood febrile convulsions and at 15 yr had an episode of transient weakness of the extremities diagnosed as Guillain-Barre disease. It is postulated that, in seizure prone individuals, lithium may induce seizures by some unknown mechanism when serum values are not in the toxic range. 3 references.

067926 Groschel, Dieter; Gerstein, Alan R.; Rosenbaum, Jerald M. Springfield Hospital Medical Center, 759 Chestnut Street, Springfield, Massachusetts 01107 Skin lesions as a diagnostic aid in barbiturate poisoning. ***New England Journal of Medicine.*** **283(8):409-410, 1970.**

A case history of a woman with barbiturate poisoning was presented illustrating concomitant symptomatic skin lesions, which may aid early diagnosis of barbiturate poisoning. The patient was found deeply comatose beside a bottle that had held 30 capsules of a sedative containing 100mg pentobarbital sodium and 260mg of carbromal. On admission the pulse was 80, blood pressure 80/60 and respirations 20/minute and shallow. Pupils were 4mm in diameter and fixed. She was totally areflexic, and an intratracheal tube was inserted without difficult. There were vesicles 3 to 4mm, and bullae, 2 to 3cm in size, on an erythematous base on the dorsa of the hands, around both knees and on the heels, most of which contained a clear fluid. On admission, the serum barbiturate level was 4.3mg percent. Blister fluid from a skin lesion over the tibia showed 1.8mg of barbiturate. She recovered and was discharged with all lesions healing. Although skin lesions can be observed in other comatose or dead patients they are usually quite different from the clear vesicles of barbiturate poisoning, hence these lesions may aid in the early differential diagnosis of coma due to drug ingestion. 5 references.

067934 Wang, Richard I. H.; Wiesen, Richard L. Clinical Pharmacology Service, Wood Veterans Administration Center, Milwaukee, Wisconsinn 53193 An approach to the treatment of drug abuse. ***Wisconsin Medical Journal.*** **69(5):148-150, 1970.**

An approach to the treatment of drug dependencies of the opiate type, the amphetamine type, the barbiturate type and the hallucinogen type is described. The 3 basic phases of treatment are: the control of acute toxicity, the management of detoxification and the provision for aftercare, including psychotherapy and rehabilitation. Drugs of the opiate type include heroin, Meperidine, dihydromorphinone, oxymorphone, hydroxycodone, oxycodone and morphine. This type of dependence can be treated by detoxification (using methadone in decreasing doses), maintenance (with methadone), or antagonism (cyclazocine, naloxone). After treatment, patients should be seen once a week to provide supportive therapy. Symptoms of acute amphetamine toxicity can be treated with chlorpromazine or thioridazine in doses of 50 100mg i.m. until they subside. Tricyclic antidepressants should be used

to treat accompanying depression. Psychotherapy is essential to aftercare. To detoxify barbiturate abusers, the tolerance level of the patient must be determined; this can be accomplished with increasing doses of pentobarbital which can subsequently be gradually decreased. Chloral hydrate can be used during the last phases of withdrawal to treat restlessness and agitation. Hallucinogen toxicity can be managed much the same as amphetamine toxicity. Depression, however, is not a prominent feature. Frequent flashbacks indicate phenothiazine treatment. 13 references.

067939 No author. Author address not given In diagnosis, type of reaction is more important than the drug. ***Medical World News.*** **11(15):34-35, 1970.**

The treatment of patients suffering from overdoses of illegal drugs is discussed. Heroin overdoses are treated with nalorphine or levallorphan; barbituate overdoses are treated with gastric lavage and maintainence of respiration. For amphetamine overdoses, phenothiazine treatment is advised, as it is for the rare marijuana overdose. LSD agitation is countered by chlorpromazine. With marijuana and LSD, a talk-down is often very beneficial. Drug overdose diagnosis should be based on group reactions and not on the specific causal agent.

068007 MacGregor, J. M. Department of Neurology, Groote Schuur Hospital, Cape Town, South Africa Sleep and drug overdose. ***British Medical Journal (London).*** **No. 5712:792-793, 1970.**

In a letter to the editor, an article by Oswald and Haider in a previous issue is discussed. As a result of studies of the sleep - waking pattern in subjects who had received an overdosage of certain hypnotic drugs, Oswald and Haider reported that nitrazepam is preferable to its rivals because of its safety. The author points out, however, that, in the same article, Oswald and Haider make a statement indicating that nitrazepam in overdose may impair coordination, emotional stability, and good judgment. It is objected that judgments of drug safety in overdose cannot be equated with preference, since preference must take into account the effectiveness of a drug in normal dosage for a specific purpose. It is noted that, while raised paradoxical sleep rebound may indicate prolonged turnover of proteins in the cerebrum, the same phenomenon occurs in a variety of conditions, including amphetamine withdrawal, barbiturate withdrawal, overdosage with tricyclic drugs, and electroconvulsive treatment 'overdosage.'i reference.

068153 Ridges, A. Pauline; Harper, P. Department of Medicine, University of Liverpool, Liverpool 3, England Pink spot - is it a drug artefact? ***Psychiatria Clinica (Basel).*** **3(2):101-107, 1970.**

Apparently, drugs are not responsible per se for pink spot excretion. Since pink spot has been excreted by patients who have never received any drug therapy, drugs probably are not requisites for pink spot production. Pink spot excretion is not enhanced when patients are receiving drug therapy. Of 296 patients with a variety of psychiatric disorders, all but 19 were receiving treatment (trifluoperazine, benzhexol, sodium amylobarbitone, thioridazine and chlorpromazine). The incidence of pink spot in patients receiving therapy is sometimes even decreased rather than increased. Other chromatographic abnormalities were recorded that could be distinguished from pink spot. Not only pink spot but also the incidence of a faster running pink spot, one having similar staining reactions to DMPE but with an Rf value of 0.70 as compared with 0.60 for DMPE. By chromatographic analysis, certain drugs, such as chlorpromazine and thioridazine in patients receiving these drugs, could be identified. Trifluoperazine apparently does not contribute to pink spot excretion. This drug has been equally prescribed to patients suffering from both paranoid and nonparanoid schizophrenia, whereas it is the nonparanoid schizophrenics predominantly who have been found to excrete pink spot. A chromatographic abnormality, with an Rf value of 0.70 and designated as faster running pink spot identifies groups treated with benzhexol (given as a prophylactic measure or to counteract the parkinson like symptoms which are a side effect of the phenothiazine therapy) and especially those treated with a combination of benzhexol and trifluoperazine. There was no evidence that the material which had been termed pink spot was derived from phenothiazines or their metabolites. 6 references.

068175 Dent, Michael J. W. Hatherley Nursing Home, Sidcup, England Monoamine oxidase inhibitors. ***Nursing Mirror and Midwives Journal (London).*** **130(25):22-23, 1970.**

A case history of a patient admitted to a hospital for Nardil and Tryptizol overdosage is presented. A large rise in metabolism was seen

after admission, with a corresponding rise in body temperature to 106 degrees. No specific antidote is present for either drug and treatment was symptomatic. Respiratory alkalosis also developed from Cheyne-Stokes respiration, which was relieved by Coramine (2ml, i.m.). Administration of chlorpromazine (25mg, i.m.)every 15 min lowered the body temperature after ice packs and other conventional methods had failed. Complete recovery was made in 3 days from the superlethal dose of Nardil potentiated with Tryptizol.

068181 Malacarne, P.; Dallapiccola, B. Clinica Medica, 44100 Ferrara, Italy Schizophrenia and lymphocyte mitotic capacity. *Lancet (London).* No. 7647:619, 1970.

In reference to a study by Hughes and Field (Lancet, 1969, ii, 440) reporting response to phytohemagglutinin (PHA) stimulation of lymphocytes from perphenazine treated schizophrenics, it was suggested that the abnormal response of the lymphocytes was caused by an inhibitory serum factor associated with the use of perphenazine. Maricq and coworkers, however, obtained similar results in schizophrenic patients who had not received any drug for 6 months or more. Chromosome preparations from the peripheral blood of 12 treated and 7 untreated schizophrenic patients compared with those from 8 normal controls revealed that lymphocytic mitosis was higher in the schizophrenics than in the controls. It was concluded that blood from schizophrenic patients does not contain a factor inhibiting lymphocyte mitosis; rather it would appear that in these patients some of the lymphocytes are stimulated to mitosis. 3 references.

068603 Crane, George E. Spring Grove State Hospital, Baltimore, Maryland Cardiac toxicity and psychotropic drugs. *Diseases of the Nervous System.* 31(8):534-539, 1970.

The literature of the cardiac effects of psychotropic drugs is reviewed. Therapeutic doses of thioridazine and tricyclic antidepressants cause typical electrocardiogram (EKG) changes. The same drugs, particularly in excessive doses, may produce cardiac disorder or death. Chlorpromazine and other phenothiazines appear to be less toxic. There is also the possibility that benign EKG changes will eventually lead to permanent cardiac impairment. 57 references. (Author abstract modified)

16 METHODS DEVELOPMENT

068137 No author. Author address not given Dosage schedules in general practice. *Practitioner (London).* 204(1223):719-723, 1970.

A clinical drug trial was conducted by 15 physicians who treated 64 patients in a 4 week period, with treatment determined by random selection and with crossover of treatment regimen at two weeks, to determine whether a single dose regimen or a thrice daily dose regimen was more convenient to the patient and more likely to be followed by the patient. The drug administered was fluphenazine, which has a 24 hour action in the treatment of anxiety neurosis. The subjects were of both sexes, with a ratio of 3 women to 1 man, 10 to 71 years old, and exhibiting mild to very severe anxiety symptoms. During the first and second weeks, the proportion of patients having no tablets left over was significantly higher in the group receiving medication once daily, while in the third and fourth weeks, the proportions were not significantly different. Overall there was a higher proportion of patients leaving no tablets on a once daily dosage regimen (83%) than on a thrice daily dosage regimen (67%). There was no overall significant difference in relief of symptoms between the two regimens. There were no comparative differences in drug omission with regard to sex, employment status, or initial severity of symptoms.

17 MISCELLANEOUS

067301 Avakumov, V. M.; Vikhlyayev, Yu. I. Moscow, U.S.S.R. /The metabolism of psychotropic drugs (phenothiazine and iminodibenzyl derivatives)./ Metabolizm psikhotropnykh sredstv (proizvodnyye fenotiazina i iminodibenzila). *Zhurnal Nevropatologii i Psikhiatrii imeni S.S. Korsakova (Moskva).* 70(3):444-452, 1970.

The metabolic processes of widely used drugs in psychiatric practice are reviewed. It is pointed out that qualitative and quantitative shifts of tranformation processes of some psychotropic drugs do not remain indifferent to the organism of the patient. As the result of intensity changes of separate biotransformation reactions, the therapeutic action of the drugs cannot only be lowered but also can produce conditions for the appearance of toxic products. It is possible that prolonged usage of psychiatric drugs can lead to side -effects and lower potency of the drugs. A constant control of various drug level in blood serum and concentration of basic metabolites can create a prerequisite for development of effective therapeutic regimen when one or another drug is used. 90 references.

068601 Petursson, Esra S.; Preble, Edward. Drug Addiction Research Unit, Manhattan State Hospital, New York School of Psychiatry, N. Y. The use of cyclazocine in the treatment of heroin addicts. *Diseases of the Nervous System.* 31(8):549-551, 1970.

A study describes the course of cyclazocine treatment on 62 male heroin addicts over a 2 year period. Cyclazocine is a long acting nonaddictive analgesic that acts as a narcotic antagonist in preventing morphine type drugs from reaching the receptor sites. The low toxicity and nonaddictive properties make it a relatively safe agent for treating narcotic addiction. It has been found most effective with those who have a genuine motivation to be cured. 5 references.

068987 Freund, Jack. A. H. Robbins Company, Richmond, Virginia 23220 The dilemma of drug research. *In: Merlis, S., Non-scientific constraints on medical research.* New York, Raven Press, 1970. 117 p. (p. 41-48).

Comments are made on the dilemma of drug research from the viewpoint of significant nonscientific factors influencing pharmaceutical research. One of these factors is believed to be the Food and Drug Administration and the environment in which it must operate. There is much to be learned about the appropriate design of controlled clinical trials, it is felt, and the relationship of the FDA to the technology of drug research is discussed. The rapidly increasing costs of research, as they influence drug research, are taken into account. It is believed that recognition of the influence of nonscientific factors in scientific research is the first step in a constructive approach to solving this problem; that with appropriate communication among all parties involved in the research -regulatory process, specific questions concerning newer agents may be more readily resolved; and that awareness of the limitations of methodology will lead to a more constructive approach in the determination of the clinical profiles of proposed new drugs. It is concluded that a common effort by all concerned, directed toward resolution of nonscientific restraints in research, will enable the scientific and pharmaceutical community to discover, develop, and make available, the drugs of the future. 12 references.